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REMARKS

Claims 101-144 are pending in this application. As a preliminary matter, Applicants note that claims 101-132 (elected Group XXVII) relates to GPR38(V297K). Claims 133-144 relate to the use of GPR38(V297K).¹ Thus, claims 133-144 should be prosecuted hereby with claims 101-132, since they all relate to GPR38(V297K).

Claims 101-132 are rejected under 35 U.S.C. § 101 by the Office Action for allegedly lacking “specific and substantial asserted utility or a well-established utility.” Applicants respectfully disagree with the Office Action, and assert that the claimed inventions have a well-established utility. Further, Applicants assert that the Office Action has not established a *prima facie* case for lack of a well-established utility.

The Utility Examination Guidelines (hereinafter “Guidelines”) set forth that:

If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention..., and (2) the utility is specific, substantial and credible...

[Further] Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement.”

Federal Register, Vol. 66, No.4, January 5, 2001, pages 1098-1099.

It is readily apparent that the claimed inventions directed to GPR38(V297K) have a well established utility. For example, the present specification discloses and/or one of ordinary skill knows that:

¹ Page 2 of the Office Action recites that “Claims 133-144 are directed to method of identifying candidate compounds that modulate a G protein coupled receptor comprising SEQ ID NO:30 or variants thereof.” The correct SEQ ID NO should be SEQ ID NO: 130.

- (1) non-endogenous GPR38(V297K) differs from the endogenous GPR38 by a single amino acid, and yields a constitutively active version of the endogenous GPR38;
- (2) the constitutively active GPR38(V297K) causes increased production of intracellular cAMP (e.g., Example 4 and Figure 1 of 60/123,945);
- (3) GPR38 is expressed in the thyroid;
- (4) an activated GPR38 in the thyroid would cause an increase in production of intracellular cAMP therein, since an activated GPR38 is functionally similar to a GPR38(V297K);
- (5) an increased intracellular level of cAMP in the thyroid leads to Graves' disease [*see* Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, Ninth Edition (1996) pages 1383-1409 (Exhibit A, already provided in an IDS); and
- (6) GPR38(V297K) may be used in an assay to identify an inverse agonist of GPR38, which would decrease the level of cAMP in the thyroid for the prevention of exacerbation of or for the treatment of Graves' disease.

In view of the above, a person of ordinary skill in the art would immediately appreciate that the claims directed to GPR38(V297K) have at least one well-established utility because a GPR38(V297K) may be employed in screening assays to identify, for example, inverse agonists that may be used for the prevention of exacerbation of or for the treatment of Graves' disease.

Further, the utility is **specific** because GPR38 has been specifically found in the thyroid, and the inhibition of an activated GPR38 (e.g., by an inverse agonist identified through a screening assay that employs GPR38(V297K)) leads to a decreased production of cAMP specifically in the thyroid, which in turn may be used specifically for the prevention of exacerbation of or for the treatment of Graves' disease.

The utility is also **substantial** because the prevention of exacerbation of or treatment of Graves' disease is a "real world" use. With regard to GPR38(V297K) being used in an assay to identify possible inverse agonists thereof, Applicants note that the Revised Interim Utility Guidelines Training Material (herein after "Training Material") states that "an assay method for identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use." See

page 6 of the Training Material. Exhibit B. Here, the compounds that may be identified in an assay employing GPR38(V297K) have substantial utility themselves because these compounds, e.g. inverse agonists of GPR38, may be administered for the prevention of exacerbation of or for the treatment of Graves' disease.

Moreover, the utility is **credible** because the use of GPR38(V297K) to screen for inverse agonists compounds, wherein such compounds may be administered for the prevention of exacerbation of or for the treatment of Graves' disease, is believable to a person of ordinary skill in the art, based on the totality of evidence and reasoning Applicants have provided.

MPEP §2107.02 II. B. states that once the applicants have indicated why the invention is useful (as Applicants have indicated previously and herein), then the Office personnel should review that assertion according to the standards for an asserted utility. In so reviewing, the Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to a well-established/assert utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement.

The Office Action has not provided countervailing evidence that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of the well-established/asserted utility of GPR(V297K) indicated by the Applicants. In other words, the Office Action has not established a *prima facie* case showing that GPR(V297K) cannot be used in a screening assay to identify compounds, e.g. inverse agonists, that can modulate an endogenous GPR38 for the prevention of exacerbation of or for the treatment of Graves' disease. The Guidelines set forth that:

Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility ...
The *prima facie* showing must contain the following elements:

- (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial or well established;
- (2) Support for factual findings relied upon in reaching this conclusion; and

- (3) An evaluation of all relevant evidence or record, including utilities taught in the closest prior art.

Federal Register, Vol. 66, No.4, January 5, 2001, page 1098.

The Office Action has set forth various arguments alleging lack of utility. However, as Applicants will show, these arguments do not meet the above elements to establish a *prima facie* case for lack of a well-established utility.

Office Action argues that GPR38 is an orphan receptor for which the normal physiological role is unknown, and the endogenous ligand specific for that receptor is unknown. Page 5-6 of the Office Action. Applicants note that the knowledge of normal physiological role and endogenous ligand for GPR38 is irrelevant to determining whether there is a well-established utility for GPR38(V297K). What should be relevant is that, at the time of filing of the present application, GPR38 is known to be in specific locations, e.g., the thyroid; activated GPR38 promotes the production of cAMP in the thyroid; patients suffering from Graves' disease would benefit from the reduction of cAMP in the thyroid, as discussed above; and GPR38(V297K) may be used to screen for inverse agonists that may be administered to act on the endogenous GPR38 to reduce the thyroid production of cAMP.

The Office Action argues that there is no disclosure that changing cAMP levels in the thyroid by modulating GPR38(V297K)² or GPR38 would have any effect on Graves' disease. Page 6 of the Office Action. Applicants note that either a well-established utility or an asserted specific and substantial utility is sufficient to satisfy 35 USC § 101. MPEP § 2107.02(b) indicates that even in the absence of statements asserting a specific and substantial utility, "if an invention has a well-established utility, rejections under 35 USC 101 and 35 USC 112, first paragraph, based on lack of utility should not be imposed. *In re Folkers*, 344 F.2d 970, 145 USPQ 390 (CCPA 1965)."

² Applicants note the GPR38(V297K) is not endogenous. Thus, any consideration as to whether modulation of GPR38(V297K) would have any effect on Graves' disease would be irrelevant as to the present utility analysis. The well-established utility for GPR38(V297K) is that it may be used in a screening assay to identify compounds that may modulate GPR38, for example an endogenous GPR38.

Applicants respectfully submit that one of ordinary skill would find that the utility of GRP38(V297K) is well-established. For example, the specification discloses that GPR38(V297K) may be used in an assay to identify compounds, e.g., inverse agonists thereof. Further, the specification discloses that activated GPR38 (i.e., via the GPR38(V297K) model) increases cAMP production level.³ It was known at the time of filing of the present application that GPR38 is specifically located in certain organs, e.g., thyroid. It was also known at the time of filing that increased production of cAMP in the thyroid leads to Graves' disease. *See* Goodman and Gilman's The Pharmacological Basis of Therapeutics (Exhibit A). Thus, one of ordinary skill in the art would readily recognize that a reduction of cAMP in the thyroid would prevent the exacerbation of or treat Graves' disease. Further one of ordinary skill in the art would readily recognize that the inhibition of GPR38 would reduce the level of cAMP in the thyroid, since GPR38 is specifically located in the thyroid. Moreover, one of ordinary skill in the art would readily recognize that GPR38(V297K) may be used in a screening assay to identify inverse agonists that can inhibit GPR38 in the thyroid. Thus, one of ordinary skill would find that the utility of GRP38(V297K) is well-established.

The Office Action argues that the specification discloses general functional activities of G-protein coupled receptors (GCPR), but does not disclose any activity associated with the specific GPR38(V297) of the instant invention. Page 7 of the Office Action. Contrary to the Office Action's allegation, the utility of GPR38(V297K) is **specific** because GPR38 has been specifically found in the thyroid, and the inhibition of an activated GPR38 (e.g., by an inverse agonist identified through a screening assay that employs GPR38(V297K)) leads to a decreased production of cAMP specifically in the thyroid, which in turn is specifically useful for the prevention of the exacerbation of or for the treatment of Graves' disease.

³ Figure 1 recites an 83.1% increase in activity of the non-endogenous, constitutively active version of human GPR38(V297K) (11,505 relative light units) compared with the of the endogenous GPR38 (1950 relative light units). Note that the 83% value was incorrectly calculated from the experimental data presented and is too low. Figure 1 actually represents a 490% $(11,505/1950 \times 100\% - 100\%)$ increase in activity of the non-endogenous, constitutively active version of human GPR38(V297K) compared with that of the endogenous GPR38.

The Office Action argues that the “asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a ‘real world’ context of use.” Page 8 of the Office Action. As discussed above, the Training Material states that “an assay method for identifying compounds that themselves have a ‘substantial utility’ define a ‘real world’ context of use.” See page 6 of the Training Material. Here, the compounds that may be identified in an assay employing GPR38(V297K) have substantial utility themselves because these compounds, e.g. inverse agonists of GPR38, may be administered for the prevention of exacerbation of or for the treatment of Graves’ disease.

The Office Action argues that GPR38(V297K) is a “new member” to the GCPR family, wherein the existing members have divergent functions. The Office Action further argues that “without some common biological activity for the family members, a new member would not have a specific, substantial or credible utility.” Page 9-10 of the Office Action. The fact that GPR38(V297K) may or may not be a “new member” of the GCPR family is irrelevant as to whether GPR38(V297K) has a well-established utility. Also, whether it is known or not that an activity is common to all members is irrelevant to whether GPR38(V297K) have a well-established utility. See page 9 of Office Action.

The test for whether GPR38(V297K) has a well-established utility is whether the utility is specific, substantial and credible. As discussed above, the well-established utility for GPR38(V297K) is **specific** because GPR38 has been specifically found in certain organs, e.g, the thyroid, and the inhibition of an activated GPR38 (e.g., by an inverse agonist identified through a screening assay that employs GPR38(V297K)) leads to a decreased production of cAMP specifically in the thyroid, which in turn is specifically useful for the prevention of exacerbation of or for the treatment of Graves’ disease. The utility is also **substantial** because the prevention of exacerbation of or the treatment of Graves’ disease is a “real world” use. Moreover, the utility is **credible** because the use of GPR38(V297K) to screen for inverse agonists compounds, wherein such compounds may be administered for the prevention of exacerbation of or for the treatment of Graves’ disease, is believable to a person of ordinary skill in the art, based on the totality of evidence and reasoning Applicants have provided.

The Office Action argues that “any compound could be considered a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue.” Page 10 of the Office Action. Again, GPR38(V297K) may be employed in a screening assay to identify compounds, for example inverse agonists, that may inhibit the activity of GPR38 that are localized, for example in the thyroid. Thus the compounds to be discovered in accordance with the present invention have specific sites of action, and cannot be compared to the promiscuous water or ethanol molecule.

Accordingly, Applicants respectfully request the rejections under 35 U.S.C. § 101 be withdrawn.

Claims 101-132 also stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement since the claims allegedly lack utility. In light of the arguments above, Applicants respectfully submit that those skilled in the art would recognize both the utility of the invention and how to use it. Applicants respectfully request withdrawal of the 35 U.S.C. § 112 rejection.

In conclusion, Applicants respectfully assert that a well-established utility is disclosed for GPR38(V297K). Further, the Office Action has not established a *prima facie* case to show that the asserted utility is not specific, substantial and credible.

Accordingly, Applicants respectfully request a withdrawal of the rejection under 35 U.S.C. § 101 and § 112, first paragraph. Further, Applicants assert that the claims are in condition for allowance, and respectfully request notification to that effect. Should the Office have any questions, Applicants invite the Office to contact the undersigned at (215) 665-2158 to discuss any issues unresolved by this Amendment. A Notice of Allowance is earnestly solicited.

Respectfully submitted,



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Reg. No. 46,957

Date: February 12, 2004

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Exhibit A

Goodman & Gilman

GOODMAN & GILMAN's The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

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THYROID AND ANTITHYROID DRUGS

Alan P. Farwell and Lewis E. Braverman

This chapter discusses the function of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), in growth and metabolism and the regulation of thyroid function by thyroid-stimulating hormone (TSH) secreted from the pituitary. Calcitonin, also secreted by the thyroid gland, is discussed in Chapter 61. Evaluation of free thyroxine and TSH levels as a means to assess thyroid function is provided as a prelude to the discussion of treatment of the hypothyroid patient with hormone replacement and of the hyperthyroid individual with one of a variety of antithyroid drugs, such as propylthiouracil and methimazole, and other thyroid inhibitors, including ionic inhibitors that interfere with the concentration of iodide by the thyroid gland and radioactive iodine, used both for diagnosis as well as treatment of hypothyroidism. Although disorders of the thyroid are common, effective treatment of most thyroid disorders is available.

Thyroid hormones, the only known iodine-containing compounds with biological activity, have two important functions. In developing animals and human beings, they are crucial determinants of normal development, especially in the central nervous system (CNS). In the adult, thyroid hormones act to maintain metabolic homeostasis, affecting the function of virtually all organ systems. To meet these requirements, there are large stores of preformed hormone within the thyroid gland. Metabolism of the thyroid hormones occurs primarily in the liver, although local metabolism within certain target tissues, such as the brain, also occurs. Serum concentrations of thyroid hormones are precisely regulated by the pituitary hormone, thyrotropin, in a classic negative-feedback system. The predominant actions of thyroid hormone are mediated via binding to nuclear thyroid hormone receptors and modulating transcription of specific genes. In this regard, thyroid hormones share a common mechanism of action with steroid hormones, vitamin D, and retinoids, whose receptors make up a superfamily of nuclear receptors (see Chapter 2).

Disorders of the thyroid are common. They consist of two general presentations: changes in the size or shape of the gland or changes in secretion of hormones from the gland. Thyroid nodules and goiter in the euthyroid patient are the most common endocrinopathies and can be caused by benign and malignant tumors. The presentation of overt hyper- or hypothyroidism often presents the clinician with dramatic clinical manifestations. While the diagnosis may

be clinically obvious, subtle presentations require the use of biochemical tests of thyroid function. Screening of the newborn population for congenital hypothyroidism, followed by the institution of appropriate thyroid hormone replacement therapy, has dramatically decreased the incidence of mental retardation and cretinism in the United States. Worldwide, congenital hypothyroidism due to iodine deficiency remains the major preventable cause of mental retardation.

Effective treatment of most thyroid disorders is readily available. Treatment of the hypothyroid patient is straightforward and consists of hormone replacement. There are more options for treatment of the hyperthyroid patient, including the use of antithyroid drugs to decrease hormone synthesis and secretion by the gland and destruction of the gland by the administration of radioactive iodine or by surgical removal. Treatment of thyroid disorders in general is extremely satisfying, as most patients can be either cured or have their diseases controlled (see Braverman and Utiger, 1991; Braverman and Refetoff, 1994).

THYROID

The thyroid gland is the source of two fundamentally different types of hormones. The iodothyronine hormones include thyroxine and 3,5,3'-triiodothyronine; they are essential for normal growth and development and play an important role in energy metabolism. The other known

secretory product of the thyroid, calcitonin, is produced by the parafollicular (C-) cells and is discussed in Chapter 61.

History. The thyroid gland was first described by Galen and was named "glandulae thyroidae" by Wharton in 1656. Harington (1935) reviewed the many older opinions concerning the function of this gland. Wharton thought, for example, that the viscous fluid within the follicles lubricated the trachea. He also believed that the gland was larger in women to serve a cosmetic function in giving grace to the contour of the neck. Later observers, influenced by the liberal blood supply of the gland, believed that it provided a vascular shunt for the brain. With this function in mind, Rush in 1820 expressed the belief that the larger size of the gland in women was "necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex." However, Hofrichter opposed this theory in the same year by pointing out that "If it were indeed true that the thyroid contains more blood at some times than at others, this effect would be visible to the naked eye; in this case women would certainly have long ceased to go about with bare necks, for husbands would have learned to recognize the swelling of this gland as a danger signal of threatening trouble from their better halves."

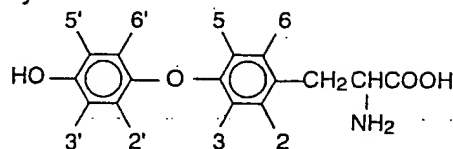
The thyroid was first recognized as an organ of importance when enlargement was observed to be associated with changes in the eyes and the heart in the condition we now call *hyperthyroidism*. It is of interest that this condition, the manifestations of which on occasion can be as striking as any in medicine, escaped description until Parry saw his first case in 1786. Parry's account was not published until 1825 and was followed in 1835 and 1840 by those of Graves and Basedow, whose names became applied to the disorder. In 1874 Gull first associated atrophy of the gland with the symptoms now known to be characteristic of thyroid deficiency, and hypofunction of the thyroid, *hypothyroidism*, in adults was known as *Gull's disease*. The term *myxedema* was applied to the clinical syndrome in 1878 by Ord in the belief that the characteristic thickening of the subcutaneous tissues was due to excessive formation of mucus.

Extirpation experiments to elucidate the function of the thyroid were at first misinterpreted because of the simultaneous removal of the parathyroids. However, the pioneer research in the late 19th century on the latter organs by Gley allowed the functional differentiation of these two endocrine glands. It was not until after calcitonin was discovered in 1961 that it was realized that the thyroid itself also was concerned with the regulation of Ca^{2+} . In 1891, Murray became the first to treat a case of hypothyroidism by injecting an extract of the thyroid gland; in the following year, Howitz, Mackenzie, and Fox independently discovered that thyroid tissue was fully effective when given by mouth.

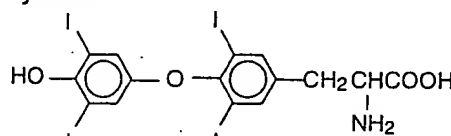
Magnus-Levy discovered the effect of the thyroid on metabolic rate in 1895; he found that Gull's disease was characterized by a low rate of metabolism and that the administration of thyroid to hypothyroid or normal individuals increased oxygen consumption.

Chemistry of Thyroid Hormones. The principal hormones of the thyroid gland are the iodine-containing amino acid derivatives of thyronine—thyroxine (T_4) and T_3 (triiodothyronine; 3,5,3'-triiodothyronine; Figure 56-1). Thyroxine was first isolated in crystalline form from a hydrolysate of thyroid by Kendall in 1915; he found that the crystalline product exerted the same physiological effects as the extract from which it was obtained. Eleven years later the structural

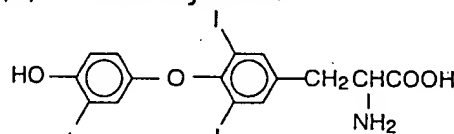
Thyronine



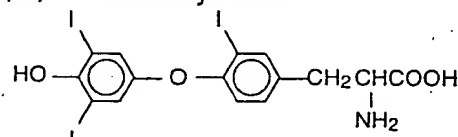
Thyroxine



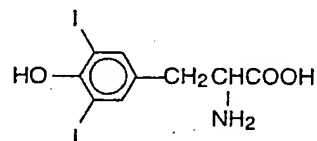
3,5,3'-Triiodothyronine



3,3',5'-Triiodothyronine



Diiodotyrosine



Iodotyrosine

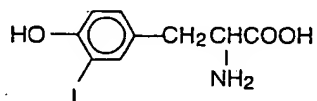


Figure 56-1. Thyronine, thyroid hormones, and precursors.

formula of thyroxine was elucidated by Harington, and in 1927 Harington and Barger synthesized the hormone.

Following the isolation and the chemical identification of thyroxine, it was generally believed that all the hormonal activity of thyroid tissue could be accounted for by its content of thyroxine. However, careful studies revealed that crude thyroid preparations possessed greater calorigenic activity than could be accounted for by their thyroxine content. The enigma was resolved with the detection, isolation, and synthesis of triiodothyronine (Gross and Pitt-Rivers, 1952; Roche *et al.*, 1952a, 1952b). Further studies revealed that triiodothyronine is qualitatively similar to thyroxine in its biological action but that it is much more potent on a molar basis (Gross and Pitt-Rivers, 1953a, 1953b).

Structure-Activity Relationship. The stereochemical nature of the thyroid hormones plays an important role in defining hormone activity. A great many structural analogs of thyroxine have been synthesized in order to define the structure-activity relationship, to detect antagonists of thyroid hormones, or to find compounds exhibiting one desirable type of activity while not showing unwanted effects.

The only significant success has been the partial separation of the cholesterol-lowering action of thyroxine analogs from their calorigenic or cardiac effects. For example, introduction of specific arylmethyl groups at the 3' position of triiodothyronine resulted in analogs that are liver-selective, cardiac-sparing thyromimetics (Leeson *et al.*, 1989). The D isomer of thyroxine was once used to lower the concentration of cholesterol in plasma, but cardiac side effects resulted in discontinuation of the clinical uses of this hormone. Newer analogs offer hope that more useful separation of these activities may yet be achievable (Underwood *et al.*, 1986; Sherman and Ladenson, 1992).

The structural requirements for a significant degree of thyroid hormone activity have been defined (see Jorgensen, 1964; Cody, 1980, 1991). The 3'-monosubstituted compounds are more active than the 3',5'-disubstituted molecules. Thus, triiodothyronine is five times more potent than thyroxine, while 3'-isopropyl-3,5-diiodothyronine has seven times the activity.

Although the chemical nature of the 3, 5, 3', and 5' substituents is important, their effects on the conformation of the molecule are even more so. In thyronine, the two rings are angulated at about 120° at the ether oxygen and are free to rotate on their axes. As depicted schematically in Figure 56-2, when the 3,5 iodines are in place, rotation of the two rings is somewhat restricted, and they tend to take up positions perpendicular to one another. While not potent, even halogen-free derivatives possess some activity if they have the proper conformation. In general, the affinity of iodothyronines for the thyroid hormone receptor parallels their biological potency (Oppenheimer *et al.*, 1987), but additional factors including affinity for plasma proteins, rate of entry into cell nuclei, and rate of metabolism can affect therapeutic potency.

Recent structure-activity correlations indicate that certain plant flavonoids that are long-standing folk remedies can exhibit antihormonal properties, including inhibition of the enzyme that catalyzes 5' (outer, or tyrosyl ring) deiodination of T₄ (type I iodothyronine 5'-deiodinase; Cody, 1991). These compounds are also potent competitors of thyroxine binding to transthyretin. Computer graphic modeling suggests that the best structural homology between thyroid hormones and flavonoids involves their respective phenolic rings.

Synthesis of Thyroid Hormones.—The synthesis of the thyroid hormones is unique, complex, and seemingly grossly inefficient. The thyroid hormones are synthesized and stored as amino acid residues of thyroglobulin, a pro-

tein constituting the vast majority of the thyroid follicular colloid. The thyroid gland is unique in storing great quantities of potential hormone in this way, and extracellular thyroglobulin can represent a large portion of the mass of the gland. Thyroglobulin is a complex glycoprotein made up of two apparently identical subunits, each with a molecular mass of 330 kDa. Interestingly, molecular cloning has revealed that thyroglobulin belongs to a superfamily of serine hydrolases, including acetylcholinesterase (see Chapter 8).

The major steps in the synthesis, storage, release, and interconversion of thyroid hormones are the following: (1) the uptake of iodide ion by the gland, (2) the oxidation of iodide and the iodination of tyrosyl groups of thyroglobulin, (3) coupling of iodotyrosine residues by ether linkage to generate the iodothyronines, (4) the proteolysis of thyroglobulin and the release of thyroxine and triiodothyronine into the blood, and (5) the conversion of thyroxine to triiodothyronine in peripheral tissues. These processes are summarized in Figure 56-3.

1. Uptake of Iodide. Iodine ingested in the diet reaches the circulation in the form of iodide. Under normal circumstances, its concentration in the blood is very low (0.2 to 0.4 µg/dl; about 15 to 30 nM), but the thyroid efficiently and actively transports the ion. As a result, the ratio of thyroid to plasma iodide concentration is usually between 20 and 50 and can far exceed 100 when the gland is stimulated. The iodide transport mechanism is inhibited by a number of ions such as thiocyanate and perchlorate (Figure 56-3). The transport system is stimulated by thyrotropin [thyroid-stimulating hormone (TSH); see below] and also is controlled by an autoregulatory mechanism. Thus, decreased stores of thyroid iodine enhance iodide uptake, and the administration of iodide can reverse this situation.

If the further metabolism of iodide is blocked by antithyroid drugs, the iodide-concentrating mechanism can be more easily studied. Thus isolated, the mechanism resembles those found in other structures that concentrate iodide, including the salivary glands, gastric mucosa, mid-portion of the small intestine, choroid plexus, skin, mammary gland, and perhaps the placenta, all of which maintain a concentration of iodide greater than that of the blood. It has been suggested that the accumulation of iodide by the placenta and the mammary gland may be of importance in providing adequate supplies for the fetus and infant, but no obvious purpose is served by the accumulation of iodide at the other sites. It is evident that the iodide-accumulating system of the thyroid is not unique to the gland and does not account for the specific function of synthesizing thyroid hormone.

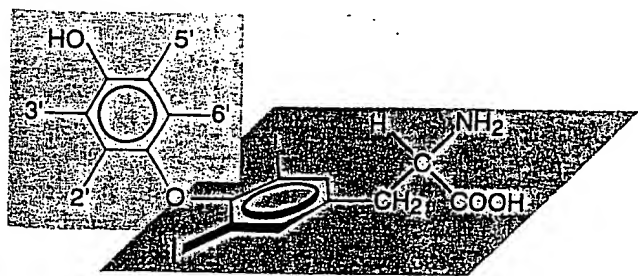


Figure 56-2. Structural formula of 3,5-diiodothyronine, drawn to show the conformation in which the planes of the aromatic rings are perpendicular to each other. (Adapted from Jorgensen, 1964. See also Cody, 1980.)

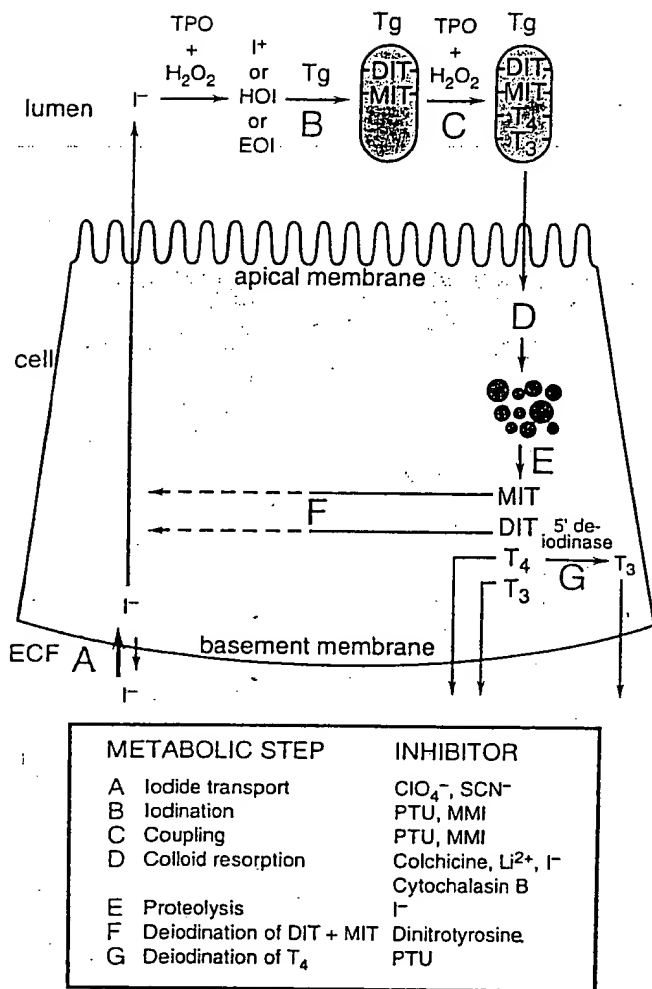


Figure 56-3. Major pathways of thyroid hormone biosynthesis and release.

Abbreviations are as follows: Tg, thyroglobulin; DIT, diiodotyrosine; MIT, monoiodotyrosine; TPO, thyroid peroxidase; HOI, hypoiodous acid; EOI, enzyme-linked species; PTU, propylthiouracil; MMI, methimazole; ECF, extracellular fluid. (Adapted from Taurog, 1991, with permission.)

2. Oxidation and Iodination. Consistent with the conditions generally necessary for halogenation of aromatic rings, the iodination of tyrosine residues requires the iodinating species to be in a higher state of oxidation than is the anion. The exact nature of the iodinating species was uncertain for many years. However, Magnusson and coworkers (1984) have provided convincing evidence that it is hypoiodate, either as hypoiodous acid (HOI) or as an enzyme-linked species (EOI).

The oxidation of iodide to its active form is accomplished by thyroid peroxidase, a heme-containing enzyme that utilizes hydrogen peroxide (H_2O_2) as the oxidant (Tau-

rog, 1991; Magnusson *et al.*, 1987). Thyroid peroxidase has been cloned and identified as an autoantigen in autoimmune thyroid disease (McLachlan and Rapoport, 1992). The peroxidase is membrane-bound and appears to be concentrated at or near the apical surface of the thyroid cell. The reaction results in the formation of monoiodotyrosyl and diiodotyrosyl residues in thyroglobulin just prior to its storage in the lumen of the thyroid follicle. It is thought that the formation of the H_2O_2 that serves as a substrate for the peroxidase occurs in close proximity to its site of utilization and involves the oxidation of reduced nicotinamide adenine di-nucleotide phosphate (NADPH). An increase in the generation of H_2O_2 may be an important facet of the mechanism by which TSH stimulates the organification of iodide in thyroid cells. This hypothesis has arisen from observations that TSH stimulates the synthesis of inositol trisphosphate and elevates cytosolic concentrations of Ca^{2+} in thyroid follicular cells (Corda *et al.*, 1985; Field *et al.*, 1987; Laurent *et al.*, 1987); the formation of H_2O_2 is stimulated by a rise in cytosolic Ca^{2+} (Takasu *et al.*, 1987).

3. Formation of Thyroxine and Triiodothyronine from Iodotyrosines. The remaining synthetic step is the coupling of two diiodotyrosyl residues to form thyroxine or of monoiodotyrosyl and diiodotyrosyl residues to form triiodothyronine. These are also oxidative reactions and appear to be catalyzed by the same peroxidase discussed above. The mechanism involves the enzymatic transfer of groups, perhaps as iodotyrosyl free radicals or positively charged ions, within thyroglobulin. Although many other proteins can serve as substrates for the peroxidase, none is as efficient as thyroglobulin in yielding thyroxine. The configuration of the protein is thus presumed to be important in facilitating this coupling reaction. Thyroxine formation occurs primarily at a location near the amino terminus of the protein, while most of the triiodothyronine is synthesized near the carboxy terminus (Dunn *et al.*, 1987). The relative rates of synthetic activity at the various sites depend on the concentration of TSH and the availability of iodide. This may account, at least in part, for the long-known relationship between the proportion of thyroxine and triiodothyronine formed in the thyroid and the availability of iodide or the relative quantities of the two iodotyrosines. For example, when there is a deficiency of iodine in rat thyroid, the ratio of thyroxine to triiodothyronine decreases from 4:1 to 1:3 (Greer *et al.*, 1968). Because triiodothyronine is at least five times as active as thyroxine and contains only three-fourths as much iodine, a decrease in the quantity of available iodine need have little impact on the effective amount of thyroid hormone elaborated by the gland. Although a decrease in the availability of iodide and

the associated increase in the proportion of monoiodotyrosine favor the formation of triiodothyronine over thyroxine, a deficiency in diiodotyrosine ultimately can impair the formation of both forms of the hormone. In addition to the coupling reaction, intrathyroidal and secreted triiodothyronine is generated by the 5'-deiodination of thyroxine (Chanoine *et al.*, 1993).

4. Secretion of Thyroid Hormones. Since thyroxine and triiodothyronine are synthesized and stored within thyroglobulin, proteolysis is an important part of the secretory process. This process is initiated by endocytosis of colloid from the follicular lumen at the apical surface of the cell. This "ingested" thyroglobulin appears as intracellular colloid droplets, which apparently then fuse with lysosomes containing the requisite proteolytic enzymes. It is generally believed that thyroglobulin must be completely broken down into its constituent amino acids for the hormones to be released. As the molecular mass of thyroglobulin is 660 kDa, and the protein is made up of about 300 carbohydrate residues and 5500 amino acid residues, only two to five of which are thyroxine, this is an extravagant process. TSH appears to enhance the degradation of thyroglobulin by increasing the activity of several thiol endopeptidases of the lysosomes (Dunn and Dunn, 1988). The endopeptidases selectively cleave thyroglobulin, yield-

ing hormone-containing intermediates that are subsequently processed by exopeptidases (Dunn *et al.*, 1991). The liberated hormones then exit the cell, presumably at its basal membrane. When thyroglobulin is hydrolyzed, monoiodotyrosine and diiodotyrosine also are liberated, but they usually do not leave the thyroid. Instead, they are selectively metabolized, and the iodine, liberated in the form of iodide, is reincorporated into protein. Normally, all this iodide is reused; however, when proteolysis is activated intensely by TSH, some of the iodide reaches the circulation, at times accompanied by trace amounts of the iodotyrosines.

5. Conversion of Thyroxine to Triiodothyronine in Peripheral Tissues. The normal daily production of thyroxine has been estimated to range between 70 and 90 μg , while that of triiodothyronine is between 15 and 30 μg . Although triiodothyronine is secreted by the thyroid, metabolism of thyroxine by sequential monodeiodination in the peripheral tissues accounts for about 80% of circulating triiodothyronine (Figure 56-4). Removal of the 5'-, or outer ring, iodine leads to the formation of triiodothyronine and is the "activating" metabolic pathway. The major site of conversion of thyroxine to triiodothyronine outside the thyroid is the liver. Thus, when thyroxine is given to hypothyroid patients in doses that pro-

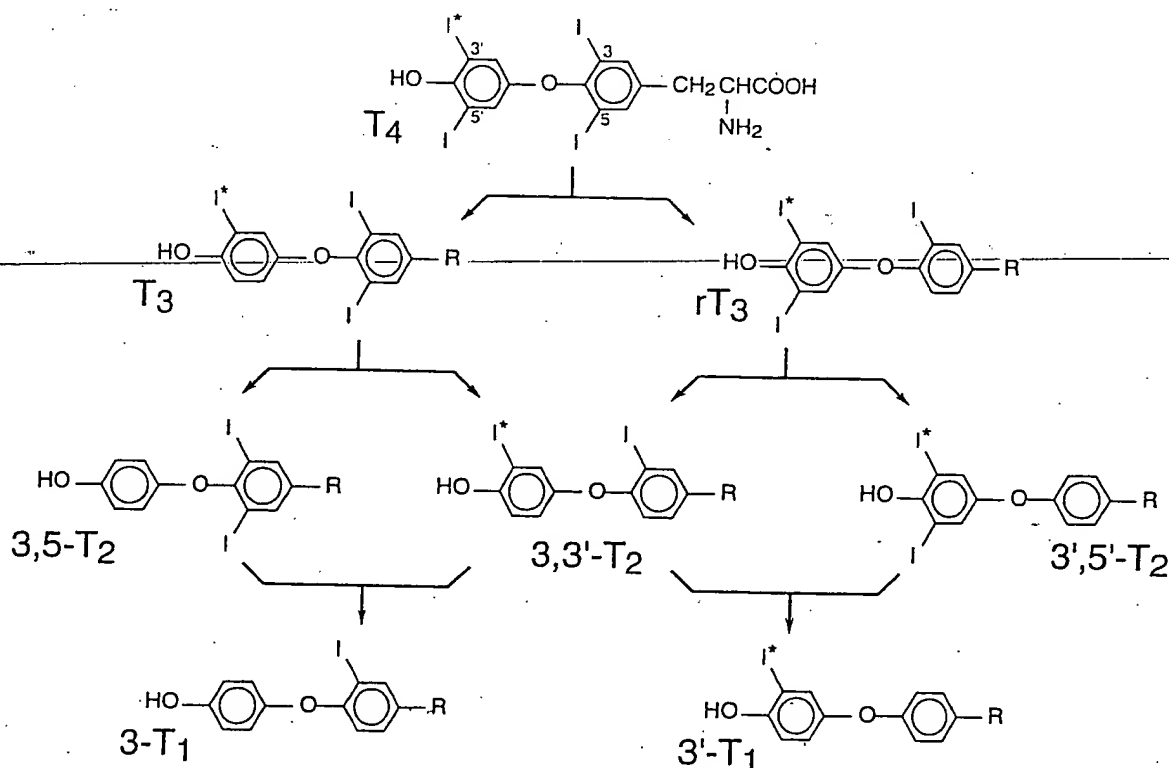


Figure 56-4. Pathways of iodothyronine deiodination.

duce normal concentrations of thyroxine in plasma, the plasma concentration of triiodothyronine also reaches the normal range. Most peripheral target tissues utilize triiodothyronine that is derived from the circulating hormone. Notable exceptions are the brain and pituitary, for which local generation of triiodothyronine is a major source for the intracellular hormone. Removal of the iodine on position 5 of the inner ring produces the metabolically inactive 3,3',5'-triiodothyronine (reverse T_3 , rT_3 ; Figure 56-1). Under normal conditions, about 41% of thyroxine is converted to triiodothyronine, about 38% is converted to reverse T_3 , and about 21% is metabolized via other pathways, such as conjugation in the liver and excretion in the bile. Normal circulating concentrations of thyroxine in plasma range from 4.5 to 11.0 $\mu\text{g/dl}$, while those of triiodothyronine are about 100-fold less (60 to 180 ng/dl).

The enzyme responsible for the conversion of thyroxine to triiodothyronine is iodothyronine 5'-deiodinase, which exists as two distinct isozymes that are differentially expressed and regulated in peripheral tissues (Figure 56-5; Leonard and Visser, 1986). Type I 5'-deiodinase (5'D-I) is found in the liver, kidney, and thyroid and generates circulating triiodothyronine that is utilized by most peripheral target tissues. Although 5'-deiodination is the major function of this isozyme, 5'D-I also catalyzes 5-deiodination. 5'D-I is inhibited by a variety of factors (Table 56-1), including the antithyroid drug, *propylthiouracil*. The decreased plasma triiodothyronine concentrations observed in nonthyroidal illnesses are a result of inhibition of 5'D-I (Kaptein, 1986) and decreased entrance of thyroxine into cells. 5'D-I is "up-regulated" in hyperthyroidism and "down-regulated" in hypothyroidism. The cloning of 5'D-I has identified the enzyme as a selenoprotein and demonstrated the presence of a selenocysteine at the active site (Berry *et al.*, 1991; Berry and Larsen, 1992). Type II 5'-deiodinase (5'D-II) is limited in distribution to the brain, pituitary, and, in the rat, brown fat and functions to supply intracellular triiodothyronine to these tissues (Visser *et al.*, 1982). 5'D-II has a much lower K_m for thyroxine than does 5'D-I (nM vs. μM

Table 56-1

Conditions and Factors That Inhibit Type I 5'-Deiodinase Activity

Acute and chronic illness
Caloric deprivation (especially carbohydrate)
Malnutrition
Glucocorticoids
β -Adrenergic blocking drugs (e.g., propranolol in high doses)
Oral cholecystographic agents (e.g., iopanoic acid, sodium ipodate)
Amiodarone
Propylthiouracil
Fatty acids
Fetal/neonatal period
Selenium deficiency

K_m values), and its activity is unaffected by propylthiouracil. 5'D-II is dynamically regulated by its substrate, thyroxine, such that elevated levels of the enzyme are found in hypothyroidism and suppressed levels are found in hyperthyroidism (Leonard *et al.*, 1981). Thus, 5'D-II appears to autoregulate the intracellular supply of triiodothyronine in the brain and pituitary. 5'D-II is a multimeric protein and is not a selenoenzyme (Safran *et al.*, 1991). Inner ring deiodination, or 5-deiodination, is primarily catalyzed by type III iodothyronine deiodinase (5D), which is found in the placenta, skin, and brain. Whether or not 5D is a selenoprotein is controversial.

Transport of Thyroid Hormones in the Blood. Iodine in the circulation is normally present in several forms, with 95% as organic iodine and approximately 5% as iodide. Most of the organic iodine is thyroxine (90% to 95%), while triiodothyronine represents a relatively minor fraction (about 5%). The thyroid hormones are transported in the blood in strong but noncovalent association with certain plasma proteins.

Thyroxine-binding globulin is the major carrier of thyroid hormones. It is an acidic glycoprotein with a molecular mass of approximately 63 kDa, and it binds one molecule of thyroxine per molecule of protein with a very high affinity (the equilibration association constant, K_a , is about 10^{10} M^{-1}). Triiodothyronine is bound less avidly. Thyroxine, but not triiodothyronine, also is bound by transthyretin (also called thyroxine-binding prealbumin). This protein is present in higher concentration than is the thyroxine-binding globulin, but it binds thyroxine and triiodothyronine with equilibrium association constants near 10^7 M^{-1} and 10^6 M^{-1} , respectively. Transthyretin has four apparently identical subunits, but has only a single high-affinity binding site. Albumin also can serve as a carrier for thyroxine when the more avid carriers are saturated. It

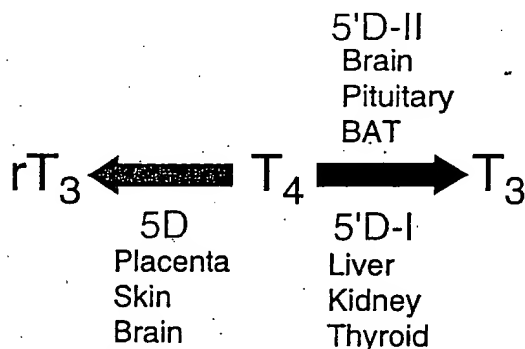


Figure 56-5. Deiodinase isozymes.

Abbreviations are as follows: 5'D-I, type I iodothyronine 5'-deiodinase; 5'D-II, type II iodothyronine 5'-deiodinase; 5D, type III iodothyronine 5-deiodinase; BAT, brown adipose tissue.

is difficult, however, to estimate its quantitative or physiological importance, with the exception of the syndrome known as *familial dysalbuminemic hyperthyroxinemia*. This is an autosomal dominant hereditary disorder characterized by the increased affinity of albumin for thyroxine (Ruiz *et al.*, 1982). Thyroxine binds also to the apolipoproteins of the high density lipoproteins, HDL₂ and HDL₃, the significance of which is unclear at present (Ben-evenga *et al.*, 1992).

Binding of thyroid hormones to plasma proteins protects the hormones from metabolism and excretion, resulting in their long half-lives in the circulation. The free (unbound) hormone is a small percentage (about 0.03% of thyroxine and about 0.3% of triiodothyronine) of the total hormone in plasma (Larsen *et al.*, 1981). The differential binding affinity for serum proteins also is reflected in the 10- to 100-fold difference in circulating hormone concentrations and half-lives of thyroxine and triiodothyronine.

Essential to understanding the regulation of thyroid function is the "free hormone" concept: only the unbound hormone has metabolic activity (Mendel, 1989). Thus, because of the high degree of binding of thyroid hormones to plasma proteins, changes in either the concentrations of these proteins or the binding affinity of the hormones for the proteins would have major effects on the total serum hormone levels. Certain drugs and a variety of pathological and physiological conditions, such as the changes in circulating concentrations of estrogens during the menstrual cycle, can alter both the binding of thyroid hormones to plasma proteins and the amounts of these proteins (Table 56-2).

Table 56-2
Factors That Alter Binding of Thyroxine to
Thyroxine-Binding Globulin

INCREASE BINDING	DECREASE BINDING
<i>Drugs</i>	
Estrogens	Glucocorticoids
Methadone	Androgens
Clofibrate	L-Asparaginase
5-Fluorouracil	Salicylates
Heroin	Mefenamic Acid
Tamoxifen	Antiseizure medications (phenytoin, carbamazepine)
	Furosemide
<i>Systemic Factors</i>	
Liver disease	Inheritance
Porphyria	Acute and chronic illness
HIV infection	
Inheritance	

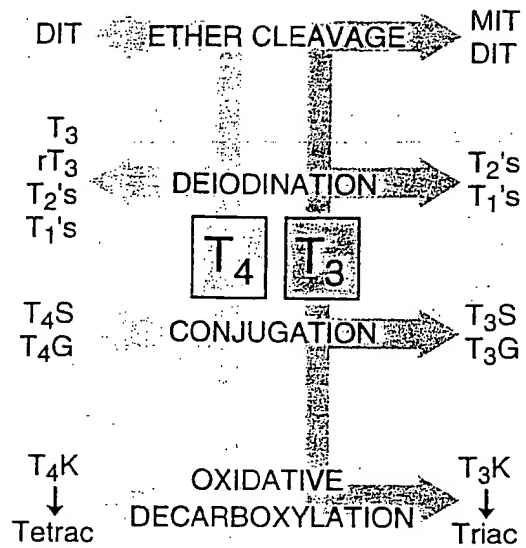


Figure 56-6. Pathways of metabolism of thyroxine (T₄ and triiodothyronine (T₃).

Abbreviations are as follows: DIT, diiodotyrosine; MIT, monoiodotyrosine; T₄S, T₄ sulfate; T₄G, T₄ glucuronide; T₃S, T₃ sulfate; T₃G, T₃ glucuronide; T₄K, T₄ pyruvic acid; T₃K, T₃ pyruvic acid; Tetrac, tetraiodothyroacetic acid; Triac, triiodothyroacetic.

However, since the pituitary responds to and regulates circulating free hormone levels, minimal changes in free hormone concentrations are seen. Laboratory tests that measure only total hormone levels, therefore, can be subject to misinterpretation. Appropriate tests of thyroid function are discussed later in this chapter.

Degradation and Excretion (Figure 56-6). Thyroxine is eliminated slowly from the body, with a half-life of 6 to 7 days. In hyperthyroidism, the half-life is shortened to 3 or 4 days, whereas in hypothyroidism it may be 9 to 10 days. These changes presumably are due to altered rates of metabolism of the hormone. In conditions associated with increased binding to plasma proteins, such as pregnancy, clearance is retarded; the reverse is observed when there is reduced protein binding of thyroid hormones or when binding to protein is inhibited by certain drugs (Table 56-2). Triiodothyronine, which is less avidly bound to protein, has a half-life of approximately 1 day.

The liver is the major site of nondeiodinative degradation of thyroid hormones; thyroxine and triiodothyronine are conjugated with glucuronic and sulfuric acids through the phenolic hydroxyl group and excreted in the bile. There is an enterohepatic circulation of the thyroid hormones; they are liberated by hydrolysis of the conjugates in the intestine and reabsorbed. A portion of the conjugated material reaches the colon unchanged, is hydrolyzed there, and is eliminated

in feces as the free compounds. In human beings, approximately 20% of thyroxine is eliminated in the stool.

As discussed above, the major route of metabolism of thyroxine is deiodination to either triiodothyronine or reverse T_3 . Triiodothyronine and reverse T_3 are deiodinated to three different diiodothyronines (see Figure 56-4), inactive metabolites that are normal constituents of human plasma. Additional metabolites (monoiodotyrosine and diiodotyrosine) in which the diphenyl ether linkage is cleaved have been detected both *in vitro* and *in vivo*.

Regulation of Thyroid Function. During the past century, it was appreciated that cellular changes occur in the anterior pituitary in association with endemic goiter or following thyroidectomy. The classical experimental observations of Cushing (1912) and the clinical observations of Simmonds (1914) established that ablation or disease of the pituitary causes thyroid hypoplasia. It eventually was determined that thyrotropes of the anterior pituitary secrete *thyrotropin*, or TSH. TSH is a glycoprotein hormone with α and β subunits analogous to those of the gonadotropins. Its structure is discussed with those of other glycoprotein hormones in Chapter 55. Although there was evidence that thyroid hormone or lack of

causes cellular changes in the pituitary, the control of secretion of TSH by the negative-feedback action of thyroid hormone was not appreciated fully until its central role in the pathogenesis of goiter was elucidated in the early 1940s. TSH is secreted in a pulsatile manner and circadian pattern, its levels in the circulation being highest during sleep at night. It is now recognized that the rate of secretion of TSH is delicately controlled by thyrotropin-releasing hormone (TRH) and the quantity of free thyroid hormones in the circulation. If extra thyroid hormone is given, transcription of the *thyrotropin gene* is decreased (see Samuels *et al.*, 1988), the secretion of TSH is suppressed, and the thyroid becomes inactive and regresses. Any decrease in the normal rate of secretion of the thyroid evokes an enhanced secretion of TSH in an attempt to stimulate the thyroid to secrete more hormone. Additional mechanisms of the effect of thyroid hormone on TSH secretion appear to be a reduction in TRH secretion by the hypothalamus and a reduction in the number of receptors for TRH on pituitary cells.

Thyrotropin-Releasing Hormone (TRH). TRH stimulates the release of preformed TSH from secretory granules and also stimulates the subsequent synthesis of both α and β subunits of TSH. Somatostatin, dopamine, and pharmacological doses of glucocorticoids inhibit TRH-stimulated TSH secretion.

TRH is a tripeptide with both terminal amino and carboxyl groups blocked (L-pyrroglutamyl-L-histidyl-L-proline amide). The mature hormone is derived from a precursor

protein that contains six copies of the tripeptide flanked by dibasic residues. TRH is synthesized by the hypothalamus and is released into the hypophysiportal circulation, where it is brought into contact with TRH receptors on thyrotropes. The binding of TRH to its receptor, a G protein-coupled receptor, elicits stimulation of the hydrolysis of polyphosphatidylinositols and activation of protein kinase C (Gershenghorn, 1986). Ultimately, TRH stimulates the synthesis and release of TSH by the thyrotope.

TRH also has been localized in the CNS in regions of the cerebral cortex, circumventricular structures, neurohypophysis, pineal gland, and spinal cord. These findings, as well as its localization in nerve endings, suggest that TRH may act as a neurotransmitter or neuromodulator outside of the hypothalamus. Administration of TRH to animals produces CNS mediated effects on behavior, thermoregulation, autonomic tone, and cardiovascular function, including increases in blood pressure and heart rate. TRH also has been identified in pancreatic islet cells and in certain parts of the gastrointestinal tract. Its physiological role there is not known.

Actions of TSH on the Thyroid. When TSH is given to experimental animals, the first effect on thyroid hormone metabolism that can be measured is increased secretion, which can be seen within minutes. All phases of hormone synthesis and release are eventually stimulated: iodide uptake and organification, hormone synthesis, endocytosis, and proteolysis of colloid. There is increased vascularity of the gland and hypertrophy and hyperplasia of thyroid cells. These effects follow the binding of TSH to its receptor on the plasma membrane of thyroid cells.

The TSH receptor is a member of the family of G protein-coupled receptors and is structurally similar to the receptors for luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (see Chapter 55; Parmentier *et al.*, 1989; Vassart and Dumont, 1992; Nagayama and Rapoport, 1992). These receptors share significant amino acid sequences and have large extracellular domains that are involved in binding of hormone.

When TSH binds to its receptor, adenylyl cyclase is stimulated and cyclic AMP levels in the cells increase. At higher concentrations than are required to stimulate cyclic AMP formation, TSH causes activation of phospholipase C, with a resultant hydrolysis of polyphosphatidylinositols, increased cytoplasmic Ca^{2+} , and activation of protein kinase C (Manley *et al.*, 1988; Van Sande *et al.*, 1990). Both the adenylyl cyclase and the phospholipase C signaling pathways appear to mediate effects of TSH on thyroid function in human beings, although the adenylyl cyclase pathway may be the sole mediating pathway in other species (see Vassart and Dumont, 1992).

Relation of Iodine to Thyroid Function. Normal thyroid function obviously requires an adequate intake of iodine; without it, normal amounts of hormone cannot be made, TSH is secreted in excess, and the thyroid becomes hyperplastic and hypertrophies. The enlarged and stimulated thyroid becomes remarkably efficient at extracting the residual traces of iodide from the blood. The iodide-concentrating mechanism develops a gradient for the ion that may be ten times normal, and in mild to moderate iodine deficiency, the thyroid usually succeeds in producing sufficient hormone. Adult hypothyroidism and cretinism may occur in more severe iodine deficiency.

In some areas of the world, simple or nontoxic goiter is prevalent because dietary iodine is not sufficient (DeLange *et al.*, 1993). Significant regions of iodine deficiency are present in Central and South America, Africa, Europe, southeast Asia, and China. The daily requirement for iodine in adults is 1 to 2 $\mu\text{g/kg}$ body weight. The United States recommended daily allowance for iodine is in the range of 40 to 120 μg for children and 150 μg for adults, with the addition of 25 μg and 50 μg recommended during pregnancy and lactation, respectively. Vegetables, meat, and poultry contain minimal amounts of iodine, whereas dairy products and fish are relatively high in iodine content (Table 56-3; Braverman, 1994). Potable water usually contains negligible amounts of iodine.

Iodine has been used empirically for the treatment of iodine-deficiency goiter for 150 years. However, its modern use was the outgrowth of the extensive studies of Marine, which culminated in the use of iodine to prevent goiter in school children in Akron, Ohio, a region where endemic iodine deficiency goiter was prevalent (Marine and Kimball, 1917). The success of these experiments led to the adoption

of iodine prophylaxis and therapy in many regions throughout the world where iodine-deficiency goiter is endemic.

The most practicable method for providing small supplements of iodine for large segments of the population is the addition of iodide or iodate to table salt; iodate is now preferred. In some countries, the use of iodized salt is required by law; in others, including the United States, the use is optional. In the United States, iodized salt provides 100 μg of iodine per gram. Other vehicles for supplying iodine to large populations who are iodine-deficient include oral or intramuscular injection of iodized oil (Thilly *et al.*, 1973), iodized drinking water supplies, iodized irrigation systems, and iodized animal feed.

Actions of Thyroid Hormones. Whereas the precise biochemical mechanisms through which thyroid hormones exert their developmental and tissue-specific effects are only beginning to be understood, the concept that most of the actions of thyroid hormones are mediated by nuclear receptors has been well accepted since the mid-1980s (for review, see Oppenheimer *et al.*, 1987; Brent, 1994). In this model, triiodothyronine binds to high-affinity nuclear receptors, which then bind to a specific DNA sequence (thyroid hormone response element) in the promoter/regulatory region of specific genes. In this fashion, triiodothyronine modulates gene transcription and, ultimately, protein synthesis. In general, the receptor without hormone is bound to the thyroid response element in the basal state. Typically, this results in repressed gene transcription, although there are some examples of constitutive gene activation. Binding by triiodothyronine may activate gene transcription by releasing the repression. Hormone-associated receptors also may have direct activation or repressive actions. Thyroxine also binds to these receptors, but it does so with a much lower affinity than triiodothyronine. It is likely that thyroxine serves principally as a "prohormone," with essentially all actions of thyroid hormone at the transcriptional level being caused by triiodothyronine.

Table 56-3
Iodine Content in Some Foodstuffs in the United States (1982-1989)

FOOD	IODINE/SERVING, μg
Ready-to-eat cereals	87
Dairy-based desserts	70
Fish	57
Milk	56
Dairy products	49
Eggs	27
Bread	27
Beans, peas, tuber	17
Meat	16
Poultry	15

SOURCE: Adapted from Braverman, 1994.

Nuclear thyroid hormone receptors were cloned in 1986 by several laboratories (Weinberger *et al.*, 1986; Sap *et al.*, 1986). They were discovered to be the cellular homologs of an avian retroviral oncoprotein, denoted *c-erb A*. There is considerable homology between the thyroid hormone receptors and the steroid nuclear receptors, and together they make up a gene superfamily that also includes the retinoic acid and vitamin D nuclear receptors (see Chapters 2 and 63; Mangelsdorf *et al.*, 1994). The thyroid hormone receptors are derived from two genes, *c-erb A α* (TR α) and *c-erb A β* (TR β), with multiple isoforms identified (Figure 56-7; Lazar, 1993). TR α_1 and TR β_1 are found in virtually all tissues that respond to thyroid hormone, whereas the other isoforms exhibit a more tissue-specific distribution. TR β_2 , for example, is expressed solely in the anterior

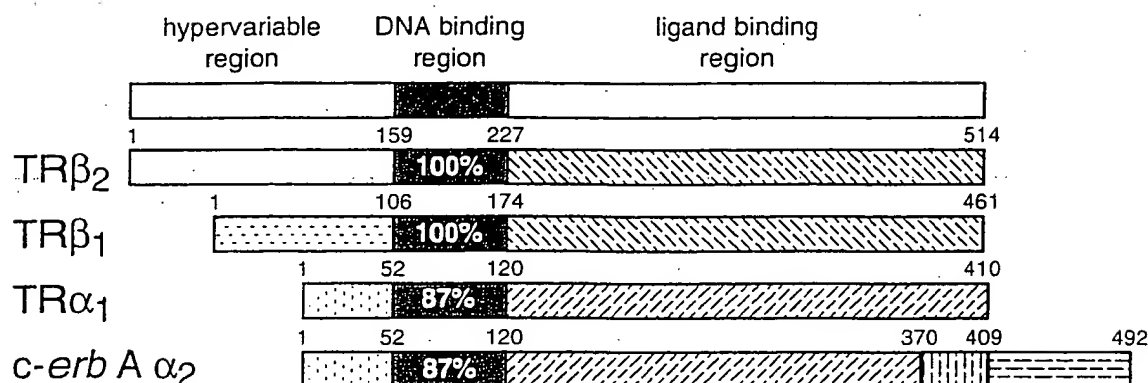


Figure 56-7. Thyroid hormone receptor isoforms.

The percent of amino acid identity in the DNA binding region is indicated. Identical patterns in the hypervariable and ligand binding regions indicate 100% homology. Three thyroid hormone receptor (TR) isoforms bind thyroid hormone (TR β_1 , TR β_2 , and TR α_1); c-erb A α_2 does not.

pituitary. c-erb A α_2 , an isoform that binds to the thyroid response element but does not bind triiodothyronine, is the most abundant isoform in brain (Strait *et al.*, 1990).

In addition to nuclear receptor-mediated actions, there are several well-characterized, nongenomic actions of thyroid hormones, including those occurring at the level of the plasma membrane (Davis *et al.*, 1989) and on the cellular cytoarchitecture (Farwell *et al.*, 1990; Siegrist-Kaiser *et al.*, 1990). In addition, there are well-characterized thyroid hormone binding sites on the mitochondria (Sterling, 1989). In several of these processes, thyroxine is the hormone that produces the response. The overall contribution of the extranuclear sites to cellular regulation by thyroid hormones is likely to be minor.

Growth and Development. As discussed above, it is generally believed that the thyroid hormones exert most if not all of their effects through control of DNA transcription and, ultimately, protein synthesis. This is certainly true for the actions of the hormones on the normal growth and development of the organism. Perhaps the most dramatic example is found in the tadpole, which is almost magically transformed into a frog by thyroid hormone. Not only does the animal grow limbs, lungs, and other terrestrial accoutrements, but the hormone also stimulates the synthesis of a host of enzymes and so influences the tail that it is digested away and used to build new tissue elsewhere.

Thyroid hormone plays a critical role in brain development (Dussault and Ruel, 1987; Porterfield and Hendrich, 1993). The appearance of functional, chromatin-bound receptors for thyroid hormone coincides with neurogenesis in the brain (Strait *et al.*, 1990). The absence of thyroid hormone during the period of active neurogenesis (up to 6 months postpartum) leads to irreversible mental retardation (cretinism) and is accompanied by multiple morphological alterations in the brain (Legrand, 1979). These severe morphological alterations result from disturbed neuronal migration, deranged axonal projections,

and decreased synaptogenesis. Thyroid hormone supplementation during the first 2 weeks of life prevents the development of these disturbed morphological changes.

Myelin basic protein, a major component of myelin, is the product of a specific gene that is regulated by thyroid hormone during development (Farsetti *et al.*, 1991). Decreased expression of myelin basic protein results in defective myelination in the hypothyroid brain. Several other minor brain-specific genes have been reported to be developmentally regulated by thyroid hormone (Porterfield and Hendrich, 1993). A common characteristic of these proteins is that their expression appears to be merely delayed in the hypothyroid animal; normal levels are eventually achieved in the adult.

The actions of thyroid hormones on protein synthesis and enzymatic activity are certainly not limited to the brain, and a large number of tissues are affected by the administration of thyroid hormone or by its deficiency. The extensive defects in growth and development that are found in cretins provide a vivid reminder of the pervasive effects of thyroid hormones in normal individuals.

Cretinism is usually classified as endemic or sporadic. *Endemic cretinism* is encountered in regions of endemic goiter and is usually caused by extreme deficiency of iodine. Goiter may or may not be present. *Sporadic cretinism* is a consequence of failure of the thyroid to develop normally or the result of a defect in the synthesis of thyroid hormone. Goiter is present if a synthetic defect is at fault.

While detectable at birth, cretinism often is not recognized until 3 to 5 months of age. When untreated, the condition eventually leads to such gross changes as to be unmistakable. The child is dwarfed, with short extremities, and is mentally retarded, inactive, uncomplaining, and listless. The face is puffy and expressionless, and the enlarged tongue may protrude through the thickened lips of the half-opened mouth. The skin may have a yellowish hue and feel doughy, and it is dry and cool to the touch. The heart rate is slow, the body temperature may be low, closure of the fontanels is delayed, and the teeth erupt late. Appetite is poor, feeding is slow and interrupted by choking, constipation is frequent, and there may be an umbilical hernia.

For treatment to be fully effective, the diagnosis must be made long before these obvious changes have come about. Screening of newborn infants for deficient function of the thyroid is carried out in the United States and in most industrialized countries. Concentrations of TSH and thyroxine are measured in blood from the umbilical cord or from a heel stick. The incidence of congenital dysfunction of the thyroid is about 1 per 4000 births (Fisher, 1991).

Calorigenic Effect. A characteristic response of homeothermic animals to thyroid hormone is increased oxygen consumption (Oppenheimer, 1991). Most peripheral tissues contribute to this response; heart, skeletal muscle, liver, and kidney are stimulated markedly by thyroid hormone. Indeed, 30% to 40% of the thyroid hormone-dependent increase in oxygen consumption can be attributed to stimulation of cardiac contractility. Several organs, including brain, gonads, and spleen, are unresponsive to the calorigenic effects of thyroid hormone. The mechanism of the calorigenic effect of thyroid hormone has been elusive. At one time, it was erroneously believed that thyroid hormone uncoupled mitochondrial oxidative phosphorylation. Thyroid hormone-dependent lipogenesis may constitute a quantitatively important energy sink, and studies in rats have demonstrated that about 4% of the increased caloric expenditure induced by thyroid hormone is accounted for by lipogenesis. A link between lipogenesis and thermogenesis is the stimulation of lipolysis by triiodothyronine. Further, thyroid hormone induces expression of several lipogenic enzymes, including malic enzyme and fatty acid synthetase. Although the entire picture is not clear, there appears to be an integrated thyroid hormone response program for regulating the set-point of energy expenditure and maintaining the metabolic machinery necessary to sustain it.

Cardiovascular Effects. Thyroid hormone influences cardiac function by direct and indirect actions; changes in the cardiovascular system are prominent clinical consequences in thyroid dysfunctional states. In hyperthyroidism, there is tachycardia, increased stroke volume, increased cardiac index, cardiac hypertrophy, decreased peripheral vascular resistance, and increased pulse pressure. In hypothyroidism, there is bradycardia, decreased cardiac index, pericardial effusion, increased peripheral vascular resistance, decreased pulse pressure, and elevations of mean arterial pressure. (For a review of the effects of thyroid hormone on the heart, see Braverman *et al.*, 1994.)

Thyroid hormones play a direct role in regulating myocardial gene expression. Triiodothyronine regulates genes encoding the isoforms of the sarcomeric myosin heavy chains by increasing the expression of the α gene and decreasing the expression of the β gene (Everett *et al.*, 1986). A thyroid hormone response element has been located in the 5' upstream region of the α myosin heavy chain gene. Triiodothyronine also upregulates the gene encoding myosin Ca^{2+} -ATPase, which plays a critical role in myocardial contraction

(Rohrer and Dillman, 1989). Regulation of these two genes results in the changes in contractility observed in hyper- and hypothyroidism.

Thyroid hormones also indirectly influence cardiac function. The sensitivity of the cardiac myocyte to catecholamines is enhanced in hyperthyroidism and depressed in hypothyroidism, possibly due to changes in expression of myocardial β -adrenergic receptors; this is the basis for the use of β -adrenergic receptor antagonists in relieving some of the cardiac manifestations of hyperthyroidism. Electrical impulse generation and conduction are increased in hyperthyroidism and decreased in hypothyroidism. These two actions likely account for the chronotropic effects of triiodothyronine. Finally, triiodothyronine causes hemodynamic alterations in the periphery that result in alterations in the chronotropic and ionotropic state of the myocardium.

Metabolic Effects. Thyroid hormones stimulate metabolism of cholesterol to bile acids, and hypercholesterolemia is a characteristic feature of hypothyroid states. Thyroid hormones have been shown to increase the specific binding of low density lipoprotein (LDL) by liver cells (Salter *et al.*, 1988), and the concentration of hepatic receptors for LDL is decreased in hypothyroidism (Scarabottolo *et al.*, 1986; Gross *et al.*, 1987). The number of LDL receptors available on the surface of hepatocytes is a strong determinant of the plasma cholesterol concentration (see Chapter 36).

Thyroid hormones enhance the lipolytic responses of fat cells to other hormones, for example, catecholamines, and elevated plasma free fatty acid concentrations are seen in hyperthyroidism. In contrast to other lipolytic hormones, thyroid hormones do not directly increase the accumulation of cyclic AMP. They may, however, regulate the capacity of other hormones to enhance the accumulation of the cyclic nucleotide by decreasing the activity of a microsomal phosphodiesterase that hydrolyzes cyclic AMP (Nunez and Correze, 1981). There also is evidence that thyroid hormones act to maintain normal coupling of the β -adrenergic receptor to the catalytic subunit of adenyl cyclase in fat cells. Fat cells from hypothyroid rats have increased concentrations of guanine nucleotide-binding regulatory proteins (G proteins) that mediate the inhibitory control of adenyl cyclase (see Chapter 2). This can account for both the decreased response to lipolytic hormones and the increased sensitivity to inhibitory regulators, such as adenosine, that are found in hypothyroidism (Ros *et al.*, 1988).

Thyrotoxicosis is an insulin-resistant state (Gottlieb and Braverman, 1994). Postreceptor defects in the liver and peripheral tissues, manifested by depleted glycogen stores and enhanced gluconeogenesis, lead to insulin insensitivity. In addition, there is increased absorption of glucose from the gut. Compensatory increases in insulin secretion result in order to maintain euglycemia. This may result in the "unmasking" of clinical diabetes in previously undiagnosed patients and an increase in the insulin requirements of diabetic patients already on insulin. Hypothyroidism results in decreased absorption of glucose from the gut and decreased insulin secretion. Peripheral glucose uptake also is slowed in hypothyroidism, although glucose utilization by the brain is unaffected. Insulin requirements are decreased in the hypothyroid patient with diabetes.

Thyroid Hyperfunction. Thyrotoxicosis is a condition caused by elevated concentrations of circulating free thyroid hormones. Various disorders of different etiologies can result in this syndrome. The term *hyperthyroidism* is restricted to those conditions in which thyroid hormones are excessively released due to gland hyperfunction. Iodine up-

take by the thyroid gland is increased, as determined by the measurement of the percent uptake of ^{123}I or ^{131}I in a 24-hour radioactive iodine uptake (RAIU) test. In contrast, thyroid inflammation or destruction resulting in excess "leak" of thyroid hormones or exogenous thyroid hormone intake results in a low 24-hour RAIU.

Graves' disease, or toxic diffuse goiter, is the most common cause of high RAIU thyrotoxicosis. It accounts for 60% to 90% of the cases, depending upon age and geographic region. Graves' disease is an autoimmune disorder characterized by hyperthyroidism, diffuse goiter, and IgG antibodies that bind to and activate the TSH receptor (Burman and Baker, 1985; Bottazzo and Doniach, 1986). This is a relatively common disorder, with an incidence of 0.02% to 0.4% in the United States. Endemic areas of iodine deficiency have a lower incidence of autoimmune thyroid disease. As with most types of thyroid dysfunction, women are affected more than men, with a ratio ranging from 5:1 to 7:1. Graves' disease is more common between the ages of 20 and 50, but may occur at any age. HLA B₈ and DR₃ haplotypes are associated with Graves' disease in Caucasians. Graves' disease is commonly associated with other autoimmune diseases. The characteristic exophthalmos associated with Graves' disease is an infiltrative ophthalmopathy and is considered an autoimmune-mediated inflammation of the periorbital connective tissue and extraocular muscle. This disorder is clinically evident with various degrees of severity in about 50% of patients with Graves' disease, but is present on radiological studies, such as ultrasound or T scan, in almost all patients. Two reviews on the pathogenesis and management of Graves' ophthalmopathy recently have been published (Burch and Wartofsky, 1993; Bahn and Heufelder, 1993).

Toxic uninodular and multinodular goiter accounts for 10% to 40% of cases of hyperthyroidism and is more common in older patients. Infiltrative ophthalmopathy is absent.

A low RAIU is seen in the destructive thyroiditides and in thyrotoxicosis resulting from exogenous thyroid hormone ingestion. Low RAIU thyrotoxicosis caused by subacute (painful) and silent (painless or lymphocytic) thyroiditis represents about 5% to 20% of all cases. Silent thyroiditis occurs in 7% to 10% of postpartum women in the United States (Roti and Emerson, 1992). Other causes of thyrotoxicosis are much less common.

Most of the signs and symptoms of thyrotoxicosis stem from the excessive production of heat and from increased motor activity and increased activity of the sympathetic nervous system. The skin is flushed, warm, and moist; the muscles are weak and tremulous; the heart rate is rapid, and the heart beat is forceful; and the arterial pulses are prominent and bounding. The increased expenditure of energy gives rise to increased appetite and, if intake is insufficient, to loss of weight. There also may be insomnia, difficulty in remaining still, anxiety and apprehension, intolerance to heat, and increased frequency of bowel movements. Angina, arrhythmias, and heart failure may be present in older patients. Some individuals may show extensive muscular wasting as a result of thyroid myopathy. Patients with long-standing undiagnosed or undertreated thyrotoxicosis may develop osteoporosis due to increased bone turnover (Baran, 1994).

Thyroid Hypofunction. Hypothyroidism, known as myxedema when severe, is the most common disorder of thyroid function. Worldwide, hypothyroidism is most often the result of iodine deficiency. In nonendemic areas,

where iodine is sufficient, chronic autoimmune thyroiditis (Hashimoto's thyroiditis) accounts for the majority of cases. Failure of the thyroid to produce sufficient thyroid hormone is the most common cause of hypothyroidism and is referred to as *primary hypothyroidism*. *Central hypothyroidism* occurs much less often and results from diminished stimulation of the thyroid by TSH because of pituitary failure (*secondary hypothyroidism*) or hypothalamic failure (*tertiary hypothyroidism*). Hypothyroidism present at birth is known as *congenital hypothyroidism* and is the most common preventable cause of mental retardation in the world. Diagnosis and early intervention with thyroid hormone replacement prevent the development of cretinism, as discussed above.

Nongoitrous hypothyroidism is associated with degeneration and atrophy of the thyroid gland. The same condition follows surgical removal of the thyroid or its destruction by radioactive iodine. Since it also may occur years after antithyroid drug therapy for Graves' disease, some have speculated that hypothyroidism can be the end stage of this disorder ("burnt-out" Graves' disease). *Goitrous hypothyroidism* occurs in Hashimoto's thyroiditis and when there is a severe defect in synthesis of thyroid hormone. When the disease is mild, it may be subtle in its presentation. By the time it has become severe, however, all of the signs are overt. The appearance of the patient is pathognomonic. The face is quite expressionless, puffy, and pallid. The skin is cold and dry, the scalp is scaly, and the hair is coarse, brittle, and sparse. The fingernails are thickened and brittle, the subcutaneous tissue appears to be thickened, and there may be true edema. The voice is husky and low-pitched, speech is slow, hearing is often faulty, and mentation is impaired and depression may be present. The appetite is poor, gastrointestinal activity is diminished, and constipation is common. Atony of the bladder is rare and suggests that the function of other smooth muscles may be impaired. The voluntary muscles are weak and the relaxation phase of the deep-tendon reflexes is delayed. The heart can be dilated, and there is frequently a pericardial effusion, although this is rarely clinically significant. There also may be pleural effusions and ascites. Anemia, most commonly normochromic, normocytic, is often present, although menstrual irregularity with menorrhagia may result in iron deficiency anemia. Patients are lethargic and tend to sleep a lot and often complain of cold intolerance.

Thyroid Function Tests. The development of radioimmunoassays and, more recently, chemiluminescent and enzyme-linked immunoassays for thyroid hormones have greatly improved the laboratory diagnosis of thyroid disorders (Surks *et al.*, 1990). However, measurement of the total hormone concentration in plasma may not give an accurate picture of the activity of the thyroid gland. The total hormone concentration changes with alterations in either the amount of thyroxine-binding globulin (TBG) or the binding affinity for hormones to TBG in plasma. Although equilibrium dialysis of undiluted serum and radioimmunoassay for free thyroxine in the dialysate represent the gold standard for determining free thyroxine concentrations, this assay is labor-intensive and typically not available in routine clinical laboratories (Nelson and Tomei, 1988). The free thyroxine index is an estimation of the free thyroxine concentration and is calculated by multiplying the total thyroxine concentra-

tion by the thyroid hormone binding ratio, which estimates the degree of saturation of TBG (Nelson and Tomei, 1989). Additional procedures for estimating free thyroxine levels include radioimmunoassay using radiolabeled analogs of thyroxine that do not perturb the thyroxine-thyroid-binding globulin as the tracer (Nelson and Weiss, 1985), and a sequential thyroxine-binding/radiolabeled thyroxine competition assay, dubbed the two-step T_4 assay. This assay correlates well with free thyroxine levels measured by the more cumbersome equilibrium dialysis determination of thyroxine concentration, yet is easily adaptable to routine clinical laboratory use (Wilke, 1986).

Estimates of free thyroxine levels should be complemented with serum measurements of TSH. In fact, in individuals whose pituitary function and TSH secretion are normal, serum measurements of TSH may be the thyroid function test of choice, because pituitary secretion of TSH is sensitively regulated in response to circulating concentrations of thyroid hormones. The American Thyroid Association has published a report outlining for clinicians a suggested approach using a limited number of tests in the laboratory diagnosis of thyroid disorders, suggesting the estimates of free thyroxine and a sensitive TSH assay (Surks *et al.*, 1990).

Serum measurements of TSH have been available since 1965 and have become the thyroid function test of choice. The first assays were single antibody radioimmunoassays and remained the standard for 20 years. These assays were useful only for diagnosing primary hypothyroidism, as a lower limit of the normal range could not be reliably measured. The first "sensitive" TSH assay was developed in 1985, utilizing a dual antibody approach. Application of this method resulted in the expansion of the assay detection limit below the normal range. Thus, any assay of this type is referred to as a *sensitive TSH assay* (Nicoloff and Spencer, 1990). A major use of the sensitive TSH assay is to differentiate between normal and thyrotoxic patients, who should exhibit suppressed TSH values. The response of TSH to an injection of synthetic TRH (TRH stimulation test) may be useful in determining pituitary or hypothalamic failure as a cause of hypothyroidism. Synthetic preparations of thyrotropin-releasing hormone (*protirelin*, RELEFACT TRH, THYPINONE) are available for injection for the TRH stimulation test.

Thyrotropin (THYTROPAR) was available as an injectable preparation made from bovine pituitaries. It is no longer available because of the high incidence of anaphylaxis. This preparation was used to test the ability of thyroid tissue to take up radioactive iodine. Recombinant human TSH (THYROGEN) soon will be available for this use (Meier *et al.*, 1994).

Therapeutic Uses of Thyroid Hormone. The major indications for the therapeutic use of thyroid hormone are for hormone replacement therapy in patients with hypothyroidism or cretinism and for TSH suppression therapy in patients with nontoxic goiter or after treatment for thyroid cancer (Roti *et al.*, 1993; Toft, 1994). Thyroid hormone therapy is not indicated for treatment of the "low T_4 syndrome" ("sick euthyroid syndrome") that is a result of nonthyroidal illness (Brent and Hershman, 1986).

The synthetic preparations of the sodium salts of the natural isomers of the thyroid hormones are available and widely used for thyroid hormone therapy. *Levothyroxine sodium* ($L-T_4$, SYNTHROID, LEVOTHROID, others) is available in tablets and as a lyophilized powder for injection. *Liothyronine sodium* ($L-T_3$) is the salt of triiodothyronine and is available in tablets (CYTOMEL) and in an in-

jectable form (TRIOSTAT). A mixture of thyroxine and triiodothyronine is marketed as *liotrix* (THYROLAR). Desiccated thyroid preparations, derived from whole animal thyroids, contain both thyroxine and triiodothyronine and have highly variable biologic activity, making these preparations much less desirable.

Thyroid Hormone Replacement Therapy. Thyroxine (levothyroxine sodium) is the hormone of choice for thyroid hormone replacement therapy because of its consistent potency and prolonged duration of action. The absorption of thyroxine occurs in the small intestine and is variable and incomplete, with 50% to 80% of the dose absorbed (Hays, 1991; Hays and Nielson, 1994). Absorption is increased when the hormone is taken on an empty stomach. In addition, certain drugs may interfere with absorption of levothyroxine in the gut, including sucralfate, cholestyramine resin, iron supplements, and aluminum hydroxide. Triiodothyronine (liothyronine sodium) may be used occasionally when a quicker onset of action is desired, as, for example, in the rare presentation of myxedema coma or for preparing a patient for ^{131}I therapy for treatment of thyroid cancer. It is less desirable for chronic replacement therapy because of the requirement for more frequent dosing, higher cost, and transient elevations of serum triiodothyronine concentrations above the normal range.

The average daily adult replacement dose of levothyroxine sodium in a 68-kg person is 112 μg . That of liothyronine sodium is 25 to 50 μg . Institution of therapy in healthy younger individuals can begin at full replacement doses. Because of the prolonged half-life of thyroxine (7 days), new steady-state concentrations of the hormone will not be achieved until 4 to 6 weeks after a change in dose. Thus, reevaluation with determination of serum TSH concentration need not be performed at intervals less than 4 to 6 weeks. The goal of thyroxine replacement therapy is to achieve a TSH value in the normal range, as overreplacement of thyroxine suppressing TSH values to the subnormal range may induce osteoporosis and cause cardiac dysfunction (Ross, 1991). In individuals over the age of 60, institution of therapy at a lower daily dose of levothyroxine sodium (25 μg per day) is indicated to avoid exacerbation of underlying and undiagnosed cardiac disease. Death due to arrhythmias has been reported during the initiation of thyroid hormone replacement therapy in hypothyroid patients. The dose can be increased at a rate of 25 μg per day every few months until the TSH is normalized. For individuals with preexisting cardiac disease, an initial dose of 12.5 μg per day, with increases of 12.5 to 25 μg per day every 6 to 8 weeks, is indicated. Daily doses of thyroxine may be interrupted periodically because of intercurrent medical or surgical illnesses that prohibit taking medications by mouth. A lapse of several days of hormone replacement is unlikely to have any significant metabolic consequences. However, if more prolonged interruption in oral therapy is necessary, levothyroxine may be given parenterally at a dose 25% to 50% less than the patient's daily oral requirements.

The decision to use levothyroxine therapy in patients with elevated serum TSH values but serum thyroxine and triiodothyronine concentrations in the normal range, a syndrome known as *subclinical hypothyroidism*, must be made on an individual basis (Cooper, 1991a). Patients with subclinical hypothyroidism and goiter, autoimmune thyroid disease, hypercholesterolemia, or symptoms of hypothyroidism may benefit from levothyroxine therapy.

The dose of levothyroxine in the hypothyroid patient who becomes pregnant often needs to be increased, perhaps due to the increased serum concentrations of thyroid-binding globulin induced by estrogen (Kaplan, 1992; Glinoe, 1993). In addition, pregnancy may "unmask" hypothyroidism in patients with preexisting autoimmune

thyroid disease or in those who reside in a region of iodine deficiency (Glinoe *et al.*, 1994). Thus, serum TSH values should be determined in the first trimester in these patients and followed each trimester in patients with documented hypothyroidism, and the levothyroxine dose adjusted to keep the serum TSH in the normal range.

Comparative Responses to Thyroid Preparations. There is no significant difference in the qualitative response of the patient with myxedema to triiodothyronine, thyroxine, or desiccated thyroid. However, there are obvious quantitative differences. Following the subcutaneous administration of a large experimental dose of triiodothyronine, a metabolic response can be detected within 4 to 6 hours, at which time the skin becomes detectably warmer and the pulse rate and temperature increase. With this dose, a 40% decrease in metabolic rate can be restored to normal in 24 hours. The maximal response occurs in 2 days or less, and the effects subside with a half-time of about 8 days. The same single dose of thyroxine exerts much less effect. However, if thyroxine is given in approximately four times the dose of triiodothyronine, a comparable elevation in metabolic rate can be achieved. The peak effect of a single dose is evident in about 9 days, and this declines to half the maximum in 11 to 15 days. In both cases the effects outlast the presence of detectable amounts of hormone; these disappear from the blood with mean half-lives of approximately 1 day for triiodothyronine and 7 days for thyroxine.

Myxedema Coma. Myxedema coma is a rare syndrome that represents the extreme expression of severe, long-standing hypothyroidism (Gavin, 1991; Smallridge, 1992). It is a medical emergency, and even with early diagnosis and treatment, the mortality rate can be as high as 60%. Myxedema coma occurs most often in elderly patients during the winter months. Common precipitating factors include pulmonary infections, cerebrovascular accidents, and congestive heart failure. The clinical course of lethargy proceeding to stupor and then coma is often hastened by drugs, especially sedatives, narcotics, antidepressants, and tranquilizers. Indeed, many cases of myxedema coma have occurred in hypothyroid patients who have been hospitalized for other medical problems.

Cardinal features of myxedema coma are: (1) hypothermia, which may be profound, (2) respiratory depression, and (3) unconsciousness. Other clinical features include bradycardia, macroglossia, delayed reflexes, and dry, rough skin. Dilutional hyponatremia is common and may be severe. Elevated plasma creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) concentrations, acidosis and anemia are common findings. Lumbar puncture reveals increased opening pressure and high protein content. Hypothyroidism is confirmed by measuring serum free thyroxine index and TSH values. Ultimately, myxedema coma is a clinical diagnosis.

The mainstay of therapy is supportive care, with ventilatory support, rewarming, correction of hyponatremia, and treatment of the precipitating incident. Because of a 5% to 10% incidence of coexisting decreased adrenal reserve in patients with myxedema coma, intravenous steroids are indicated before initiating thyroxine therapy. Parenteral administration of thyroid hormone is necessary due to uncertain absorption through the gut. With intravenous preparations of both levothyroxine and liothyronine now available, a reasonable approach is an initial intravenous loading dose of 200 to 300 μg of levothyroxine with a second dose of 100 μg given 24 hours later. Simultaneously with the initial dose of levothyroxine, some clinicians recommend adding liothyronine at a dose of 10 μg intravenously every 8 hours until the patient is stable and conscious. The dose of

thyroid hormone should be adjusted on the basis of hemodynamic stability, the presence of coexisting cardiac disease, and the degree of electrolyte imbalance.

Treatment of Cretinism. Success in the treatment of cretinism depends upon the age at which therapy is started. Because of this, newborn screening for congenital hypothyroidism is routine in the United States, Canada, and many other countries around the world. In cases that do not come to the attention of physicians until retardation of development is clinically obvious, the detrimental effects of thyroid hormone deficiency on mental development will not be overcome. If, on the other hand, therapy is instituted within the first few weeks of life, normal physical and mental development is almost always achieved. Prognosis also depends on the severity of the hypothyroidism at birth and may be worse for babies with thyroid agenesis. The most critical need for thyroid hormone is during the period of myelination of the central nervous system that occurs about the time of birth. To rapidly normalize the serum thyroxine concentration in the congenitally hypothyroid infant, an initial daily dose of levothyroxine of 10 to 15 $\mu\text{g}/\text{kg}$ is recommended (Fisher, 1991). This dose will increase the total serum thyroxine concentration to the upper half of the normal range in most infants within 1 to 2 weeks. Individual levothyroxine doses are adjusted at 4- to 6-week intervals during the first 6 months, at 2-month intervals during the 6- to 18-month period, and at 3- to 6-month intervals thereafter to maintain serum thyroxine concentrations in the 10 to 16 $\mu\text{g}/\text{dl}$ range and serum TSH values below 20 mU/l. The free thyroxine levels should be kept in the upper normal or elevated range. Assessments that are important guides for appropriate hormone replacement include physical growth, motor development, bone maturation, and developmental progress.

Nodular Thyroid Disease. Nodular thyroid disease is the most common endocrinopathy. The prevalence of clinically apparent nodules is 4% to 7% in the United States, with the frequency increasing throughout adult life. When ultrasound and autopsy data are included, the prevalence of thyroid nodules approaches 50% by age 60. As with other forms of thyroid disease, nodules are more frequent in women. Nodules have been estimated to develop at a rate of 0.1% per year. In individuals exposed to ionizing radiation, the rate of nodule development is 20-fold higher. While the presence of a nodule raises the question of a malignancy, only 8% to 10% of patients with thyroid nodules have thyroid cancer. About 12,000 new cases of thyroid cancer are diagnosed annually, with about 1000 deaths from the disease per year. However, many more people have clinically silent thyroid cancer, as up to 35% of thyroids removed at autopsy or at surgery harbor a small (<1 cm) occult papillary cancer.

The evaluation of the patient with nodular thyroid disease includes a careful physical examination, biochemical analysis of thyroid function, and assessment of the malignant potential of the nodule (Mazzaferri, 1993; Gharib and Goellner, 1993). The latter often includes examination of a fine-needle aspiration biopsy of the nodule and radioisotope scanning with ^{123}I or ^{131}I to determine if a particular nodule is functioning. TSH suppressive therapy with levothyroxine is an option for the patient diagnosed with a benign solitary nodule. The rationale behind levothyroxine therapy is that the benign nodule will either stop growing or decrease in size after TSH stimulation of the thyroid gland has been suppressed. The success rate of such therapy ranges from 0 to 68% in different studies. Identification of those patients who are most likely to benefit from thyroid hormone therapy can be achieved through measurement of the serum TSH concentration and radioisotope scanning. Suppression therapy will be of no value if thyroid nodule autonomy exists, as evidenced by a subnormal TSH value and all isotope uptake in the nodule. Functioning nodules are the most likely to respond to suppression therapy. However, once TSH concentrations are suppressed, a repeat radioisotope scan (suppression scan) should be obtained. If significant

uptake persists on a suppression scan, the nodule is nonsuppressible and levothyroxine therapy should be discontinued. Suppression therapy needs to be considered carefully in older patients or in those with coronary artery disease, and, in general, such therapy should be avoided in these patients. Hypofunctioning nodules are much less likely to respond to suppression therapy. However, a 6- to 12-month trial of levothyroxine suppression is reasonable. If levothyroxine is administered, therapy should be continued for as long as the nodule is decreasing in size. Once the size of a nodule remains stable for a 6- to 12-month period, therapy may be discontinued and the nodule observed for recurrent growth. Any nodule that grows while on suppression therapy should be rebiopsied and/or surgically excised.

ANTITHYROID DRUGS AND OTHER THYROID INHIBITORS

A large number of compounds are capable of interfering, directly or indirectly, with the synthesis, release, or action of thyroid hormones (Table 56-4). Several are of great clinical value for the temporary or extended control of hyperthyroid states. These will be discussed in detail. Others are primarily of research or toxicological interest and are only mentioned briefly. The major inhibitors may be classified

into four categories: (1) antithyroid drugs, which interfere directly with the synthesis of thyroid hormones; (2) ionic inhibitors, which block the iodide transport mechanism; (3) high concentrations of iodine itself, which decrease release of thyroid hormones from the gland and also may decrease hormone synthesis; and (4) radioactive iodine, which damages the gland with ionizing radiation. Adjuvant therapy with drugs that have no specific effects on thyroid gland hormonogenesis is useful in controlling the peripheral manifestations of thyrotoxicosis. These drugs include: inhibitors of the peripheral deiodination of thyroxine to the active hormone, triiodothyronine; β -adrenergic receptor antagonists; and Ca^{2+} channel blockers. The antithyroid drugs have been reviewed by Green (1991) and Cooper (1984). Adrenergic agents are discussed more fully in Chapter 10 and Ca^{2+} channel blockers in Chapter 35.

Antithyroid Drugs

The antithyroid drugs that have clinical utility are the thioureylens, which belong to the family of thionamides. Propylthiouracil may be considered as the prototype.

Table 56-4
Antithyroid Compounds

PROCESS AFFECTED	EXAMPLES OF INHIBITORS
Active transport of iodide	Complex anions: perchlorate, fluoborate, pertechnetate, thiocyanate
Iodination of thyroglobulin	Thionamides: propylthiouracil, methimazole, carbimazole Thiocyanate Aniline derivatives; sulfonamides
Coupling reaction	Iodide Thionamides Sulfonamides ?All other inhibitors of iodination
Hormone release	Lithium salts Iodide
Iodotyrosine deiodination	Nitrotyrosines
Peripheral iodothyronine deiodination	Thiouracil derivatives Oral cholecystographic agents Amiodarone
Hormone excretion/inactivation	Inducers of hepatic drug-metabolizing enzymes: phenobarbital, rifampin, carbamazepine, phenytoin
Hormone action	Thyroxine analogs Amiodarone ?Phenytoin

SOURCE: Adapted from Green, 1991.

History. Studies on the mechanism of the development of goiter began with the observation that rabbits fed a diet composed largely of cabbage often developed goiters. This result was probably due to the presence of precursors of the thiocyanate ion in cabbage leaves (see below). Later, two pure compounds were shown to produce goiter, sulfaguanidine and phenylthiourea.

Investigation of the effects of thiourea derivatives revealed that rats became hypothyroid despite hyperplastic changes in their thyroid glands that were characteristic of intense thyrotropic stimulation. After treatment was begun, no new hormone was made, and the goitrogen had no visible effect upon the thyroid gland following hypophysectomy or the administration of thyroid hormone. This suggested that the goiter was a compensatory change resulting from the induced state of hypothyroidism and that the primary action of the compounds was to inhibit the formation of thyroid hormone (Astwood, 1945). The therapeutic possibilities of such agents in hyperthyroidism were evident, and the substances so used became known as *antithyroid drugs*.

Structure-Activity Relationship. The two goitrogens found in the early 1940s proved to be prototypes of two different classes of antithyroid drugs. These two, with one later addition, made up three general categories into which the majority of the agents can be assigned: (1) *thioureylenes* include all the compounds currently used clinically (Figure 56-8); (2) *aniline derivatives*, of which the sulfonamides make up the largest number, embrace a few substances that have been found to inhibit thyroid hormone synthesis; and (3) *polyhydric phenols*, such as resorcinol, which have caused goiter in human beings when applied to the abraded skin. A few other compounds, mentioned briefly below, do not fit into any of these categories.

Thiourea and its simpler aliphatic derivatives and heterocyclic compounds containing a thioureylene group make up the majority of the known antithyroid agents that are effective in human beings. Although most of them incorporate the entire thioureylene group, in some a nitrogen atom is replaced by oxygen or sulfur so that only the thioamide group is common to all. Among the heterocyclic compounds, active representatives are the sulfur derivatives of imidazole, oxazole, hydantoin, thiazole, thiadiazole, uracil, and barbituric acid.

L-5-Vinyl-2-thioxazolidone (goitrin) is responsible for the goiter that results from consuming turnips or the seeds or green parts of cruciferous plants. These plants are eaten by cows, and the compound is found in cow's milk in areas of endemic goiter in Finland; it is about as active as propylthiouracil in human beings. VanEtten (1969) has reviewed the chemistry of naturally occurring goitrogens.

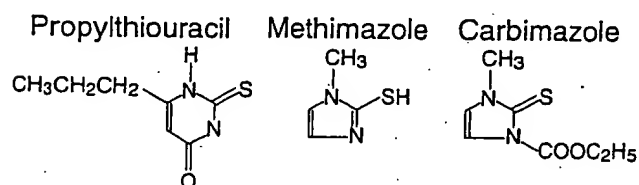


Figure 56-8. Antithyroid drugs of the thiamide type.

As the result of industrial exposure, toxicological studies, or clinical trials for various purposes, several other compounds have been noted to possess antithyroid activity (Gaitan, 1989; McKinney and Waller, 1994). Thiopental and oral hypoglycemic drugs of the sulfonylurea class have weak antithyroid action in experimental animals. This is not significant at usual doses in human beings. However, antithyroid effects in human beings have been observed from dimercaprol, aminoglutethimide, and lithium salts. Amiodarone, the iodine-rich drug used in the management of cardiac arrhythmias, has complex effects on thyroid function (Gammage and Franklyn, 1987). In areas of iodine sufficiency, amiodarone-induced hypothyroidism is not uncommon, whereas in iodine-deficient regions, amiodarone-induced thyrotoxicosis predominates, whether because of the excess iodine or the thyroiditis induced by the drug. Amiodarone is a potent inhibitor of iodothyronine deiodination, resulting in decreased conversion of thyroxine to triiodothyronine. In addition, its major metabolite, desmethylamiodarone, decreases binding of triiodothyronine to its nuclear receptors.

Mechanism of Action. The mechanism of action of the thioureylene drugs has been thoroughly discussed by Taurog (1991). Antithyroid drugs inhibit the formation of thyroid hormones by interfering with the incorporation of iodine into tyrosyl residues of thyroglobulin; they also inhibit the coupling of these iodotyrosyl residues to form iodothyronines. This implies that they interfere with the oxidation of iodide ion and iodotyrosyl groups. Taurog (1976) proposed that the drugs inhibit the peroxidase enzyme, thereby preventing oxidation of iodide or iodotyrosyl groups to the required active state. Subsequent studies have confirmed that this is, indeed, the mechanism of action and that the antithyroid drugs bind to and inactivate the peroxidase only when the heme of the enzyme is in the oxidized state (Davidson *et al.*, 1978; Engler *et al.*, 1982). Over a period of time, the inhibition of hormone synthesis results in the depletion of stores of iodinated thyroglobulin as the protein is hydrolyzed and the hormones are released into the circulation. Only when the preformed hormone is depleted and the concentrations of circulating thyroid hormones begin to decline do clinical effects become noticeable.

There is some evidence that the coupling reaction may be more sensitive to an antithyroid drug, such as propylthiouracil, than is the iodination reaction (Taurog, 1991). This may explain why patients with hyperthyroidism respond well to doses of the drug that only partially suppress organification.

When Graves' disease is treated with antithyroid drugs, the concentration of thyroid-stimulating immunoglobulins in the circulation often decreases. This has prompted some to propose that these agents act as immunosuppressants. Burman and Baker (1985) point out that perchlorate, which acts by an entirely different mechanism, also decreases thyroid-stimulating immunoglobu-

lins, suggesting that improvement in hyperthyroidism may, itself, favorably affect the abnormal humoral immune state.

In addition to blocking hormone synthesis, propylthiouracil inhibits the peripheral deiodination of thyroxine to triiodothyronine. Methimazole does not have this effect and can antagonize the inhibitory effect of propylthiouracil. Although the quantitative significance of this inhibition has not been established, it does provide a theoretical rationale for the choice of propylthiouracil over other antithyroid drugs in the treatment of severe hyperthyroid states or of thyroid storm. In this acute situation, a decreased rate of conversion of circulating thyroxine to triiodothyronine would be beneficial.

Absorption, Metabolism, and Excretion. The antithyroid compounds currently used in the United States are *propylthiouracil* (6-*n*-propylthiouracil) and *methimazole* (1-methyl-2-mercaptoimidazole; TAPAZOLE). In Great Britain and Europe, *carbimazole* (NEO-MERCAZOLE), a carbethoxy derivative of methimazole, is available, and its antithyroid action is due to its conversion to methimazole after absorption. Some pharmacological properties of propylthiouracil and methimazole are shown in Table 56-5. Measurements of the course of organification of radioactive iodine by the thyroid show that absorption of effective amounts of propylthiouracil follows within 20 to 30 minutes of an oral dose. They also show that the duration of action of the compounds used clinically is brief. The effect of a dose of 100 mg of propylthiouracil begins to wane in 2 to 3 hours, and even a 500-mg dose is completely inhibitory for only 6 to 8 hours. As little as 0.5 mg of methimazole similarly decreases the organification of radioactive iodine in the thyroid gland, but a single dose of 10 to 25 mg is needed to extend the inhibition to 24 hours.

The half-life of propylthiouracil in plasma is about 75 minutes, whereas that for methimazole is 4 to 6 hours. The drugs appear to be concentrated in the thyroid, and methimazole, derived from the metabolism of carbimazole, accumulates after carbimazole is administered. Drugs and metabolites appear largely in the urine.

Although both propylthiouracil and methimazole cross the placenta and also can be found in milk, methimazole does so to a greater degree than propylthiouracil (Marchant *et al.*, 1977). The use of these drugs during pregnancy is discussed below.

Untoward Reactions. The incidence of side effects from propylthiouracil and methimazole as currently used is relatively low. The overall incidence as compiled from published cases by early investigators was 3% for propylthiouracil and 7% for methimazole, with 0.44% and 0.12% of cases, respectively, developing the most serious reaction, agranulocytosis (Meyer-Gessner *et al.*, 1994). The development of agranulocytosis with methimazole may be dose-related, but no such relationship exists with propylthiouracil. Further observations have found little, if any, difference in side effects between these two agents, and suggest that an incidence of agranulocytosis of approximately 1 in 500 is a maximal figure. Agranulocytosis usually occurs during the first few weeks or months of therapy but may occur later. Because agranulocytosis can develop rapidly, periodic white-cell counts usually are of little help. Patients should immediately report the development of sore throat or fever, which usually heralds the onset of this reaction. Agranulocytosis is reversible upon discontinuation of the offending drug, and the administration of recombinant human granulocyte colony-stimulating factor may hasten recovery (Magner *et al.*, 1994). Mild granulocytopenia, if noted, may be due to thyrotoxicosis

Table 56-5
Selected Pharmacokinetic Features of Antithyroid Drugs

	PROPYLTHIOURACIL	METHIMAZOLE
Plasma protein binding	~75%	Nil
Plasma half-life	75 minutes	~4-6 hours
Volume of distribution	~20 liters	~40 liters
Metabolism of drug during illness		
Severe liver disease	Normal	Decreased
Severe kidney disease	Normal	Normal
Transplacental passage	Low	Increased
Levels in breast milk	Low	Increased

SOURCE: Adapted from Cooper, 1991b.

or may be the first sign of this dangerous drug reaction. Caution and frequent leukocyte counts are then required.

The most common reaction is a mild, occasionally purpuric, urticarial papular rash. It often subsides spontaneously without interrupting treatment, but it sometimes calls for the administration of an antihistamine or changing to another drug, because cross-sensitivity is uncommon. Other less frequent complications are pain and stiffness in the joints, paresthesias, headache, nausea, skin pigmentation, and loss of hair. Drug fever, hepatitis, and nephritis are rare, although abnormal liver function tests are not infrequent with higher doses of propylthiouracil.

Therapeutic Uses. The antithyroid drugs are used in the treatment of *hyperthyroidism* in the following three ways: (1) as definitive treatment, to control the disorder in anticipation of a spontaneous remission in Graves' disease; (2) in conjunction with radioactive iodine, to hasten recovery while awaiting the effects of radiation; and (3) to control the disorder in preparation for surgical treatment. There is no uniformity of opinion as to which form of treatment is the most desirable (Soloman *et al.*, 1990), and this is often influenced by a variety of considerations, as discussed below.

The usual starting dose for propylthiouracil is 100 mg every 8 hours or 150 mg every 12 hours. When doses larger than 300 mg daily are needed, further subdivision of the time of administration to every 4 to 6 hours is occasionally helpful. Methimazole is effective when given as a single daily dose because of its relatively long plasma and intrathyroidal half-life, as well as its long duration of action. Failures of response to daily treatment with 300 to 400 mg of propylthiouracil or 30 to 40 mg of methimazole are most commonly due to noncompliance. Delayed responses also are noted in patients with very large goiters or those in whom iodine in any form has been given beforehand. Once euthyroidism is achieved, usually within 12 weeks, the dose of antithyroid drug can be reduced.

Response to Treatment. Hyperthyroidism may be of two kinds—Graves' disease and hyperthyroidism from one or more hyperfunctioning thyroid nodules; whichever the cause, the hyperthyroidism seems to respond to antithyroid drugs in the same way. After treatment is instituted, there is usually a latent period of several weeks before improvement is clearly manifest. In patients with large goiters and particularly if they are nodular, the response may be slower. The rate of response is determined by the quantity of stored hormone, the rate of turnover of hormone in the thyroid, the half-life of the hormone in the periphery, and the completeness of the block in synthesis imposed by the dosage given. When large doses are continued, and sometimes with the usual dose, hypothyroidism may develop as a result of overtreatment. The earliest signs of hypothyroidism call for a reduction in dose; if by chance they have advanced to the point of discomfort, thyroid hormone can be given to hasten recovery. A full dose of levothyroxine can be given. The lower maintenance dose of antithyroid drug discussed above is instituted for continued therapy. Concomitant use of levothyroxine therapy along with antithyroid drugs has been reported to increase rates of remission of Graves' disease in Japan (Hashizume *et al.*, 1991). However, this may represent differences in patient population, as well as the higher iodine intake in Japan.

After treatment is initiated, patients should be examined and thyroid function tests (serum free thyroxine index and total triiodothy-

ronine concentrations) measured every 2 to 4 months. Once euthyroidism is established, follow-up every 4 to 6 months is reasonable.

Control of the hyperthyroidism usually is associated with a decrease in goiter size, but if the thyroid enlarges, hypothyroidism probably has been induced. When this occurs, the new enlargement is quickly reversed by giving thyroid hormone. The presumption is, therefore, that TSH is secreted in excessive amounts in response to the hypothyroidism and can be suppressed by thyroid hormone.

Remissions. The antithyroid drugs have been used in many patients to control the hyperthyroidism of Graves' disease until a remission occurs. Early investigators reported that 50% of patients so treated for 1 year remained well without further therapy for long periods, perhaps indefinitely. More recent reports have indicated that a much smaller percentage of patients sustain remissions after such treatment. Increased dietary iodine has been implicated in the latter, less favorable rates.

Unfortunately, there is no way of predicting before treatment is begun which patients will eventually achieve a lasting remission and who will relapse. It is clear that a favorable outcome is unlikely when the disorder is of long standing, the thyroid is quite large, and various forms of treatment have failed. To complicate the issue further, it is thought that remission and eventual hypothyroidism may represent the natural history of Graves' disease.

During treatment, a fairly certain sign that a remission may have taken place is a reduction in the size of the goiter. The persistence of goiter usually indicates failure, unless the patient becomes hypothyroid. Another favorable indication is continued freedom from all signs of hyperthyroidism when the maintenance dose is small. Finally, a decrease in thyroid-stimulating immunoglobulins, suppression of ^{123}I thyroid uptake when thyroxine or triiodothyronine is given, and a normal serum TSH response to TRH are helpful in predicting a remission in some patients, although these tests are not routinely carried out.

The Therapeutic Choice. Because antithyroid drug therapy, radioactive iodine, and subtotal thyroidectomy all are effective treatments for Graves' disease, there is no worldwide consensus among endocrinologists as to the best approach to therapy. Two recent reviews have discussed available options (Franklyn, 1994; Klein *et al.*, 1994). Prolonged drug therapy of Graves' disease in anticipation of a remission is most successful in patients with small goiters or mild hyperthyroidism. Those with large goiters or severe disease usually require definitive therapy with either surgery or radioactive iodine (^{131}I). Radioactive iodine remains the treatment of choice of many endocrinologists in the United States (Soloman *et al.*, 1990). A relative contraindication for radioactive iodine therapy is coexisting, severe ophthalmopathy, since worsening of ophthalmopathy has been reported after radioactive iodine (Tallstedt *et al.*, 1992; Kung *et al.*, 1994). Depleting the thyroid gland of preformed hormone by treatment with antithyroid drugs is advisable in older patients prior to therapy with radioactive iodine so as to prevent a severe exacerbation of the hyperthyroid state during the subsequent development of radiation thyroiditis. Subtotal thyroidectomy is advocated for Graves' disease in young patients with large goiters, children who are allergic to antithyroid drugs, pregnant women (usually in the second trimester) who are allergic to antithyroid drugs, and patients who prefer surgery over antithyroid drugs or radioactive iodine. Radioactive iodine or surgery is indicated for definitive therapy in toxic nodular goiter, since remissions following antithyroid drug therapy do not occur.

Thyrotoxicosis in Pregnancy. Thyrotoxicosis occurs in about 0.2% of pregnancies and is caused most frequently by Graves' disease. Antithyroid drugs are the treatment of choice; radioactive iodine is clearly contraindicated (Momotani *et al.*, 1986). Propylthiouracil is preferred over methimazole because of its lower transplacental passage (Marchant *et al.*, 1977). Propylthiouracil dosage should be minimized to keep the serum free thyroxine index in the upper half of the normal range or slightly elevated. As pregnancy progresses, Graves' disease often improves. Indeed, it is not uncommon for patients to require daily propylthiouracil doses of less than 100 mg or to have antithyroid drugs discontinued by the end of pregnancy. Therefore, the propylthiouracil dose should be reduced, and maternal thyroid function should be monitored frequently to decrease chances of fetal hypothyroidism. Relapse or worsening of Graves' disease is common after delivery, and patients should be monitored closely. Propylthiouracil is the drug of choice in nursing women; the very small amounts of the drug that appear in breast milk do not appear to affect thyroid function in the suckling baby. A review of antithyroid drug therapy in pregnancy has been published recently (Mandel *et al.*, 1994).

Adjuvant Therapy. Several drugs that have no intrinsic antithyroid activity are useful in the symptomatic treatment of thyrotoxicosis. β -Adrenergic receptor antagonists (Chapter 10) are effective in antagonizing the catecholaminergic effects of thyrotoxicosis by reducing the tachycardia, tremor, and stare and relieving palpitations, anxiety, and tension. Either propranolol, 20 to 40 mg four times daily, or atenolol, 50 to 100 mg daily, is usually given initially. Propranolol and esmolol can be given intravenously if needed. Propranolol, in addition to its β -adrenergic receptor antagonist action, has weak inhibitory effects on peripheral conversion of thyroxine to triiodothyronine. Ca^{2+} channel blockers (diltiazem, 60 to 120 mg four times daily) can be used to control tachycardia and decrease the incidence of supraventricular tachyarrhythmias (see Chapter 35). These drugs should be discontinued once the patient is euthyroid.

Other drugs that are useful in the rapid treatment of the severely thyrotoxic patient are agents that inhibit the peripheral conversion of thyroxine to triiodothyronine. Dexamethasone (0.5 to 1 mg two to four times daily) and the iodinated radiological contrast agents, iopanoic acid (TELEPAQUE, 500 to 1000 mg once daily) and sodium ipodate (ORAGRAFIN, 500 to 1000 mg once daily) are effective in the short term but should not be used chronically.

Preoperative Preparation. Patients must be rendered euthyroid prior to subtotal thyroidectomy as definitive treatment for hyperthyroidism to reduce operative morbidity and mortality. It is possible to bring virtually 100% of patients to a euthyroid state; the operative mortality in these patients in the hands of an experienced thyroid surgeon is extremely low. Prior treatment with antithyroid drugs usually is successful in rendering the patient euthyroid for surgery. Iodide is added to the regimen for 7 to 10 days prior to surgery to decrease the vascularity of the gland, making it less friable and decreasing the difficulties for the surgeon. In the patient who is either allergic to antithyroid drugs or is noncompliant, a euthyroid state usually can be achieved by treatment with iopanoic acid, dexamethasone, and propranolol for 5 to 7 days prior to surgery. All of these drugs should be discontinued after surgery.

Thyroid Storm. Thyroid storm is an uncommon but life-threatening complication of thyrotoxicosis in which a severe form of the disease is usually precipitated by an intercurrent medical problem (Smallridge, 1992; Gavin, 1991). It occurs in untreated or partially treated thyrotoxic patients. Precipitating factors associated with thy-

rotoxic crisis include: infections, stress, trauma, thyroidal or non-thyroidal surgery, diabetic ketoacidosis, labor, heart disease, and radioactive iodine treatment.

Clinical features are similar to those of thyrotoxicosis, but more exaggerated. Cardinal features include fever (temperature usually over 38.5°C) and tachycardia out of proportion to the fever. Nausea, vomiting, diarrhea, agitation, and confusion are frequent presentations. Coma and death may ensue in up to 20% of patients. Thyroid function abnormalities are similar to those found in uncomplicated hyperthyroidism. Therefore, thyroid storm is primarily a clinical diagnosis.

Treatment includes supportive measures such as intravenous fluids, antipyretics, cooling blankets, and sedation. Antithyroid drugs are given in large doses. Propylthiouracil is preferred over methimazole because of its additional action of impairing peripheral conversion of thyroxine to triiodothyronine. The recommended initial dose of propylthiouracil is 200 to 300 mg every 6 hours. Propylthiouracil and methimazole can be administered by nasogastric tube or rectally if necessary. Neither of these preparations is available for parenteral administration in the United States.

Iodides, orally or intravenously, are used after the first dose of an antithyroid drug has been administered (see below). The radiographic contrast dyes may be used to block thyroid hormone release (as a result of the iodide released from these agents) and to inhibit thyroxine to triiodothyronine conversion. β -Adrenergic receptor antagonists, such as propranolol and esmolol, and Ca^{2+} channel blockers may also be used to control tachyarrhythmias. Dexamethasone (0.5 to 1 mg intravenously every 6 hours) is recommended both as supportive therapy and as an inhibitor of conversion of thyroxine to triiodothyronine. Finally, treatment of the underlying precipitating illness is essential.

Ionic Inhibitors

The term *ionic inhibitors* designates the substances that interfere with the concentration of iodide by the thyroid gland. The effective agents are themselves anions that in some ways resemble iodide; they are all monovalent, hydrated anions of a size similar to that of iodide. The most studied example, *thiocyanate*, differs from the others qualitatively; it is not concentrated by the thyroid gland, and in large amounts it inhibits the organification of iodine. Thiocyanate is produced following the enzymatic hydrolysis of certain plant glycosides. Thus, certain foods (e.g., cabbage) and cigarette smoking result in an increased concentration of thiocyanate in the blood and urine, as does the administration of sodium nitroprusside. Dietary precursors of thiocyanate may be a contributing factor in endemic goiter in certain parts of the world, especially in Central Africa, where the intake of iodine is very low (Delange *et al.*, 1993).

Among other anions, *perchlorate* (ClO_4^-) is ten times as active as thiocyanate. Although perchlorate can be used to control hyperthyroidism, it has caused fatal aplastic anemia when given in excessive amounts (2 to 3 g daily). Over the past few years, however, perchlorate in doses of 750 mg daily has been used in the treatment of Graves' disease and amiodarone-induced thyrotoxicosis. Perchlorate can be used to "discharge" inorganic iodide from the thyroid gland in a diagnostic test of organification. Other ions, selected on the basis of their size, also have been found to be active; fluoborate (BF_4^-) is as effective as perchlorate. Lithium has a multitude of effects on thyroid function; its principal effect is decreased secretion of thyroxine and triiodothyronine (Takami, 1994).

Iodide

Iodide is the oldest remedy for disorders of the thyroid gland. Before the antithyroid drugs were used, it was the only substance available for control of the signs and symptoms of hyperthyroidism. Its use in this way is indeed paradoxical, and the explanation for this paradox is still incomplete.

Mechanism of Action. High concentrations of iodide appear to influence almost all important aspects of iodine metabolism by the thyroid gland (*see* Ingbar, 1972). The capacity of iodide to limit its own transport has been mentioned above. Acute inhibition of the synthesis of iodotyrosines and iodothyronines by iodide also is well known (the *Wolff-Chaikoff effect*). This transient, 2-day inhibition is observed only above critical concentrations of intracellular rather than extracellular concentration of iodide. With time there is "escape" from this inhibition that is associated with an adaptive decrease in iodide transport and a lowered intracellular iodide concentration (Braverman and Ingbar, 1963). The mechanism of the Wolff-Chaikoff effect may involve inhibition of inositol phosphate signaling pathways within the thyrocyte (Corvilain *et al.*, 1994).

A very important clinical effect of high plasma iodide concentration is an inhibition of the release of thyroid hormone. This action is rapid and efficacious in severe thyrotoxicosis. The effect is exerted directly on the thyroid gland, and it can be demonstrated in the euthyroid subject and experimental animals as well as in the hyperthyroid patient. Recent studies in a cultured thyroid cell line suggest that some of the inhibitory effects of iodide on thyrocyte proliferation may be mediated by actions of iodide on crucial regulatory points in the cell cycle (Smerdely *et al.*, 1993).

In euthyroid individuals, the administration of doses of iodide from 1.5 to 150 mg daily results in small decreases in plasma thyroxine and triiodothyronine concentrations and small compensatory increases in serum TSH values, with all values remaining in the normal range. However, euthyroid patients with a history of a wide variety of underlying thyroid disorders may develop iodine-induced hypothyroidism when exposed to large amounts of iodine present in many commonly prescribed drugs (Table 56-6), and these patients do not escape from the acute Wolff-Chaikoff effect (Braverman, 1994). Among the disorders that predispose patients to iodine-induced hypothyroidism are: treated Graves' disease, Hashimoto's thyroiditis, postpartum lymphocytic thyroiditis, subacute painful thyroiditis, and lobectomy for benign nodules. The most commonly prescribed iodine-containing drugs are certain expectorants, topical antiseptics, and radiology contrast agents.

Response to Iodide in Hyperthyroidism. The response to iodides in patients with hyperthyroidism is often striking and rapid. The effect is usually discernible within 24 hours, and the basal metabolic rate may fall at a rate comparable to that following thyroidectomy. This provides evidence that the release of hormone into the circulation is rapidly blocked. Furthermore, thyroid hormone synthesis also may be decreased. The maximal effect is attained after 10 to 15 days of continuous therapy, when the signs and symptoms of hyperthyroidism may have greatly improved.

The changes in the thyroid gland have been studied in detail; vascularity is reduced, the gland becomes much firmer, the cells become smaller, colloid reaccumulates in the follicles, and the quantity of bound iodine increases. The changes are those that would be expected if the excessive stimulus to the gland had somehow been removed or antagonized.

Unfortunately, iodide therapy usually does not completely control the manifestations of hyperthyroidism, and after a variable period of time, the beneficial effect disappears. With continued treatment, the hyperthyroidism may return in its initial intensity or may become even more severe than it was at first. It is for this reason that, when iodide was the only agent available for the treatment of hyperthyroidism, its use was usually restricted to preparation of the patient for thyroidectomy.

Therapeutic Uses. The uses of iodide in the treatment of hyperthyroidism are in the preoperative period in preparation for thyroidectomy and, in conjunction with antithyroid drugs and propranolol, in the treatment of thyrotoxic crisis. Prior to surgery, iodide is sometimes employed alone, but more frequently it is used after the hyperthyroidism has been controlled by an antithyroid drug. It is then given during the 7 to 10 days immediately preceding the operation. Optimal control of hyperthyroidism is achieved if antithyroid drugs are first given alone. If iodine also is given from the beginning, variable responses are observed; sometimes the effect of iodide predominates, storage of hormone is promoted, and prolonged antithyroid treatment is required before the hyperthyroidism is controlled. These clinical observations may be explained by the ability of iodide to prevent the inactivation of thyroid peroxidase by antithyroid drugs (Taurog, 1991).

Another use of iodine is to protect the thyroid from radioactive iodine fallout following a nuclear accident. Because the uptake of radioactive iodine is inversely proportional to the serum concentration of stable iodine, the administration of 30 to 100 mg of iodide daily will markedly decrease the thyroid uptake of radioisotopes of iodine. Following the Chernobyl nuclear reactor accident in 1986, approximately 10 million children and adults in Poland were given stable iodide to block the thyroid exposure to radioactive iodine from the atmosphere and from dairy products from cows that ate contaminated grass (Naumann and Wolf, 1993).

The dosage or form in which iodide is administered bears little relationship to the response achieved in hyperthyroidism, provided not less than the minimal effective amount is given; this dosage is

Table 56-6
Commonly Used Iodine-Containing Drugs

DRUGS	IODINE CONTENT
Oral or local	
Amiodarone	75 mg/tablet
Calcium iodide (e.g., CALCIDRINE SYRUP)	26 mg/ml
Iodoquinol (diiodohydroxyquin)	134-416 mg/tablet
Echothiophate iodide ophthalmic solution	5-41 μ g/drop
Hydriodic acid syrup	13-15 mg/ml
Iodochlorhydroxyquin	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol	15 mg/tablet
Idoxuridine ophthalmic solution	18 μ g/drop
Kelp	0.15 mg/tablet
Potassium iodide (e.g., QUADRINAL)	145 mg/tablet
Lugol's solution	6.3 mg/drop
Niacinamide hydroiodide + potassium iodide (e.g., IODO-NIACIN)	115 mg/tablet
PONARIS nasal emollient	5 mg/0.8 ml
Saturated solution of potassium iodide	38 mg/drop
Parenteral preparations	
Sodium iodide, 10% solution	85 mg/ml
Topical antiseptics	
Iodoquinol (diiodohydroxyquin) cream	6 mg/g
Iodine tincture	40 mg/ml
Iodochlorhydroxyquin cream	12 mg/g
Iodoform gauze	4.8 mg/100 mg gauze
Povidone iodine	10 mg/ml
Radiology contrast agents	
Diatrizoate meglumine sodium	370 mg/ml
Propyliodone	340 mg/ml
Iopanoic acid	333 mg/tablet
Iodate	308 mg/capsule
Iothalamate	480 mg/ml
Metrizamide	483 mg/ml before dilution
Iohexol	463 mg/ml

SOURCE: Adapted from Braverman, 1994.

6 mg per day in most, but not all, patients. *Strong iodine solution* (Lugol's solution) is widely used and consists of 5% iodine and 10% potassium iodide, which yields a dose of 6.3 mg of iodine per drop. The iodine is reduced to iodide in the intestine before absorption. Saturated solution of potassium iodide also is available, containing 38 mg per drop. Typical doses include 3 to 5 drops of Lugol's solution or 1 to 3 drops of saturated solution of potassium iodide 3 times a day. These doses have been determined empirically and are far in excess of that needed.

Untoward Reactions. Occasional individuals show marked sensitivity to iodide or to organic preparations that contain iodine when they are administered intravenously. The onset of an acute reaction

may occur immediately or several hours after administration. Angioedema is the outstanding symptom, and swelling of the larynx may lead to suffocation. Multiple cutaneous hemorrhages may be present. Also, manifestations of the serum-sickness type of hypersensitivity, such as fever, arthralgia, lymph node enlargement, and eosinophilia, may appear. Thrombotic thrombocytopenic purpura and fatal periarteritis nodosa attributed to hypersensitivity to iodide have also been described.

The severity of symptoms of chronic intoxication with iodide (*iodism*) is related to the dose. The symptoms start with an unpleasant brassy taste and burning in the mouth and throat, as well as soreness of the teeth and gums. Increased salivation is noted. Coryza, sneezing, and irritation of the eyes with swelling of the eyelids are

commonly observed. Mild iodism simulates a "head cold." The patient often complains of a severe headache that originates in the frontal sinuses. Irritation of the mucous glands of the respiratory tract causes a productive cough. Excess transudation into the bronchial tree may lead to pulmonary edema. In addition, the parotid and submaxillary glands may become enlarged and tender, and the syndrome may be mistaken for mumps parotitis. There also may be inflammation of the pharynx, larynx, and tonsils. Skin lesions are common, and vary in type and intensity. They usually are mildly acneiform and distributed in the seborrheic areas. Rarely, severe and sometimes fatal eruptions (ioderma) may occur after the prolonged use of iodides. The lesions are bizarre, resemble those caused by bromism, a rare problem, and, as a rule, involute quickly when iodide is withdrawn. Symptoms of gastric irritation are common; and diarrhea, which is sometimes bloody, may occur. Fever is occasionally observed, and anorexia and depression may be present. The mechanisms involved in the production of these derangements remain unknown.

Fortunately, the symptoms of iodism disappear spontaneously within a few days after stopping the administration of iodide. The renal excretion of I^- can be increased by procedures that promote Cl^- excretion (e.g., osmotic diuresis, chloruretic diuretics, and salt loading). These procedures may be useful when the symptoms of iodism are severe.

Radioactive Iodine

Chemical and Physical Properties. Although iodine has several radioactive isotopes, greatest use has been made of ^{131}I . It has a half-life of 8 days, and, therefore, over 99% of its radiation is expended within 56 days. Its radioactive emissions include both γ rays and β particles. The short-lived radionuclide of iodine, ^{123}I , is primarily a γ -emitter with a half-life of only 13 hours. This permits a relatively brief exposure to radiation during thyroid scans.

Effects on the Thyroid Gland. The chemical behavior of the radioactive isotopes of iodine is identical to that of the stable isotope, ^{127}I . ^{131}I is rapidly and efficiently trapped by the thyroid, incorporated into the iodoamino acids, and deposited in the colloid of the follicles, from which it is slowly liberated. Thus, the destructive β particles originate within the follicle and act almost exclusively upon the parenchymal cells of the thyroid with little or no damage to surrounding tissue. The γ radiation passes through the tissue and can be quantified by external detection. The effects of the radiation depend upon the dosage. When small tracer doses of ^{131}I are administered, thyroid function is not disturbed. However, when large amounts of radioactive iodine gain access to the gland, the characteristic cytotoxic actions of ionizing radiation are observed. Pyknosis and necrosis of the follicular cells are followed by disappearance of colloid and fibrosis of the gland. With properly selected doses of ^{131}I , it is possible to destroy the thyroid gland completely without detectable

injury to adjacent tissues. After smaller doses, some of the follicles, usually in the periphery of the gland, retain their function.

Therapeutic Uses. *Sodium iodide I 131* (IODOTOPE THERAPEUTIC) is available as a solution or in capsules containing essentially carrier-free ^{131}I suitable for oral administration. *Sodium iodide I 123* is available for scanning procedures. Radioactive iodine finds its widest use in the treatment of hyperthyroidism and in the diagnosis of disorders of thyroid function. Discussion will be limited to the uses of ^{131}I .

Hyperthyroidism. Radioactive iodine is highly useful in the treatment of hyperthyroidism, and in many circumstances it is regarded as the therapeutic procedure of choice for this condition (Soloman *et al.*, 1990; for review, see Farrar and Toff, 1991). The use of iodide as treatment for hyperthyroidism, however, may preclude, for months, treatment and certain imaging studies with radioactive iodine.

Dosage and Technique. ^{131}I is administered orally, and the effective dose differs for individual patients. It depends primarily upon the size of the thyroid, the iodine uptake of the gland, and the rate of release of radioactive iodine from the gland subsequent to its deposition in the colloid. To determine these variables insofar as possible, many investigators administer a tracer dose of ^{131}I and calculate the ^{131}I accumulated by the gland and the rate of loss therefrom. The weight of the gland is estimated by palpation. From these data, the dose of isotope necessary to provide from 7000 to 10,000 rad per gram of thyroid tissue is determined. Even when dosage is controlled in this manner, it is difficult to predict the response of an individual to a given amount of the isotope. For these reasons, the optimal dose of ^{131}I , expressed in terms of microcuries taken up per gram of thyroid tissue, varies in different laboratories from 80 to 150 μCi . The usual total dose is 4 to 15 mCi. Lower-dosage ^{131}I therapy (80 $\mu Ci/g$ thyroid) has been advocated to reduce the incidence of subsequent hypothyroidism. While the incidence of hypothyroidism in the early years after such therapy is lower, many patients with late hypothyroidism may go undetected, and the ultimate incidence of hypothyroidism is probably no less than with the larger doses (Glennon *et al.*, 1972). In addition, relapse of the hyperthyroid state, or initial failure to alleviate the hyperthyroid state, is increased in patients receiving lower doses of ^{131}I .

Course of Disease. The course of hyperthyroidism in a patient who has received an optimal dose of ^{131}I is characterized by progressive recovery. It is very unusual for any tenderness to be noted in the thyroid region, and most observers have failed to detect any exacerbation of hyperthyroidism from loss of hormone from the damaged gland in patients whose preformed hormone stores have been depleted by antithyroid drug therapy. Beginning a few weeks after treatment, the symptoms of hyperthyroidism gradually abate over a period of 2 to 3 months. If therapy has been inadequate, the necessity for further treatment is apparent within 6 to 12 months.

Depending to some extent upon the dosage schedule adopted, one-half to two-thirds of patients are cured by a single dose, one-third to one-fifth require two doses, and the remainder require three or more doses before the disorder is controlled. Patients treated with larger doses of ^{131}I almost always develop hypothyroidism within a few months.

Propranolol or antithyroid drugs or both can be used to hasten the control of hyperthyroidism while awaiting the full effects of the radioactive iodine. However, the antithyroid drugs should be withheld for a few days before and after the therapeutic dose of ^{131}I .

Advantages. The advantages of radioactive iodine in the treatment of Graves' disease are many. No death as a direct result of the use of the isotope has been reported, and only by a gross miscalculation of dose could such an event conceivably occur. In the non-pregnant patient, no tissue other than the thyroid is exposed to sufficient ionizing radiation to be detectably altered. Nevertheless, the continuing concern about potential effects of radiation on germ cells prompts some endocrinologists to advocate antithyroid drugs or surgery in younger patients who are acceptable operative risks (Cooper, 1991b). Hypoparathyroidism is a small risk of surgery. With radioactive iodine treatment, the patient is spared the risks and discomfort of surgery. The cost is low, hospitalization is not required, and patients can indulge in their customary activities during the entire procedure.

Disadvantages. The chief disadvantage of the use of radioactive iodine is the high incidence of delayed hypothyroidism that is induced. Even when elaborate procedures are used to estimate iodine uptake and gland size, a certain percentage of patients will be overtreated. A distressing feature of this complication is its rising prevalence with the passage of time; the longer the interval after treatment, the higher the incidence. Several analyses of groups of patients treated 10 or more years previously suggest that the eventual rate may exceed 80%. However, it now appears that the incidence of hypothyroidism also increases progressively after subtotal thyroidectomy, and such failure of glandular function is probably part of the natural progression of Graves' disease, no matter what the therapy.

Although it is often said that hypothyroidism is not a serious complication because it can be treated so easily with thyroid hormone, its onset may be insidious and overlooked for some time. Also, once diagnosed it is difficult to ensure that patients who need the hormone actually take it. Hypothyroidism is obviously a serious complication deserving of painstaking care to make certain that optimal replacement therapy is provided.

Another disadvantage of radioactive iodine therapy is the long period of time that is sometimes required before the hyperthyroidism is controlled. When a single dose is effective, the response is most satisfactory; however, when multiple doses are needed, it may be many months or a year or more before the patient is well. This disadvantage can be largely overcome if the initial dose is sufficiently large. Other disadvantages include possible worsening of ophthalmopathy after treatment, although this is controversial (Tallstedt *et al.*, 1992). Although extremely rare, there have been reported cases of thyroid storm after therapy with ^{131}I .

Indications. The clearest indication for this form of treatment is hyperthyroidism in older patients and in those with heart disease. Radioactive iodine also is the best form of treatment when Graves' disease has persisted or recurred after subtotal thyroidectomy and when prolonged treatment with antithyroid drugs has not led to remission. Finally, radioactive iodine is indicated in patients with toxic nodular goiter, since the disease does not go into spontaneous remission. The risk of inducing hypothyroidism is less in nodular goiter than in Graves' disease, perhaps because of the normal progression of the latter and the preservation of nonautonomous thyroid tissue in the former. Usually, larger doses of radioactive iodine are required in the treatment of toxic nodular goiter than in the treatment of Graves' disease.

Contraindications. The risk of causing neoplastic changes in the thyroid gland has been constantly under consideration since radioactive iodine was first introduced, and only small numbers of children have been treated in this way. Indeed, many clinics have declined to treat younger patients for fear of causing cancer and have reserved radioactive iodine for patients over some arbitrary age, such as 25 or 30 years. Since experience with ^{131}I is now vast, these age limits are lower than they were in the past. There is no evidence that radioactive iodine therapy for Graves' disease has caused thyroid or any other form of cancer in adults, although the very large doses that are used to treat cancer (*see below*) may be associated with an increased incidence of leukemia. The use of radioactive iodine during pregnancy is contraindicated; after the first trimester the fetal thyroid would concentrate the isotope and thus suffer damage, but even during the first trimester radioactive iodine is best avoided because there may be adverse effects of radiation on fetal tissues.

Metastatic Thyroid Carcinoma. While most well-differentiated thyroid carcinomas accumulate very little iodine, stimulation of iodine uptake with TSH often is used effectively to treat metastases. Follicular carcinomas, which account for 10% to 15% of thyroid malignancies, are especially amenable to this treatment. Currently, endogenous TSH stimulation is evoked by withdrawal of thyroid hormone replacement therapy in patients previously treated with near-total thyroidectomy with or without radioactive ablation of residual thyroid tissue. In the future, injection of recombinant human TSH may be sufficient (Meier *et al.*, 1994). Total body ^{131}I scanning when the patient is hypothyroid ($\text{TSH} > 35 \text{ mIU/L}$), should be performed to identify metastatic disease or residual thyroid bed tissue. Depending upon the residual uptake, or the presence of metastatic disease, an ablative dose of ^{131}I ranging from 30 to 150 mCi is administered, and a repeat total body scan is obtained 1 week later. The precise amount of ^{131}I needed to treat residual tissue and metastases is controversial.

Suppressive therapy with levothyroxine is indicated in all patients after treatment for thyroid cancer. The goal of therapy is to keep serum TSH levels in the subnormal range (Burmeister *et al.*, 1992). Follow-up evaluation every 6 months is reasonable, along with determination of serum thyroglobulin concentrations. A rise in serum thyroglobulin concentration is often the first indication of recurrent disease. Prognosis in patients with thyroid cancer depends upon the pathology and size of the tumor and is generally worse in the elderly (*see Farid et al.*, 1994). Overall, the vast majority of patients with thyroid cancer will not die of their disease. Papillary cancer is not an aggressive tumor. It metastasizes locally and has a 10-year survival rate of greater than 90%. Lymph node metastases at the time of diagnosis do little to alter the prognosis. Follicular cancer is more aggressive and can metastasize via the bloodstream. Still, prognosis is fair, and long-term survival is common. Anaplastic cancer is the exception, as it is highly malignant with survival usually less than 1 year.

Diagnostic Uses. Tracer studies with radioactive iodine have found wide application in studies of disorders of the thyroid gland. Measurement of the thyroïdal accumulation of a tracer dose is helpful in the diagnosis of hyperthyroidism, hypothyroidism, and goiter, and the response of the thyroid to TSH or to suppression by thyroid hormone can be evaluated in this way. Following the administration of a tracer dose, the pattern of localization in the thyroid gland can be depicted by a special scanning apparatus, and this technique is sometimes useful in defining thyroid nodules as functional ("hot") or nonfunctional ("cold") and in finding ectopic thyroid tissue and occasionally metastatic thyroid tumors.

For further discussion of diseases of the thyroid, see Chapter 334 in *Harrison's Principles of Internal Medicine*, 13th ed., McGraw Hill, New York, 1994.

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Exhibit B

diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

- A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.
- B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101.)
- C. A method of assaying for or identifying a material that itself has no "specific and/or substantial utility".
- D. A method of making a material that itself has no specific, substantial and credible utility.